Impact of Keratoconus in the Better Eye and the Worse Eye on Vision-Related Quality of Life

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Purpose. We assessed the impact of keratoconus disease indicators in the better eye and worse eye on quality of life (QoL) using the Vision and Quality of Life Index (VisQoL) multi-attribute utility instrument (MAUI).

Methods. ?tlsb -.01w?>Patients with keratoconus completed the six-item VisQoL utility measure. Visual acuity was assessed using a logMAR chart, and corneal thickness and the keratometric values were measured by using Scheimpflug imaging (Pentacam). Four indicators of keratoconus disease status were considered in this study, namely best corrected visual acuity (BCVA), average front corneal curvature (Front Km), thinnest corneal location (TCL), and spherical equivalent refractive error (SE). As keratoconus is an asymmetric condition, we considered the disease parameters separately for the better eye and the worse eye. The association between the four keratoconus indicators and VisQoL utilities was assessed using multivariate linear regression.

Results. A total of 170 patients with keratoconus completed the VisQoL. Patients' median age was 33 (IQR = 18) years (range, 14–75 years) and 58% (n = 99) were males. The median VisQoL utility value was 0.60 (IQR, 0.46; range, 0.02–0.99). The VisQoL utilities reduced with increasing age ($\rho = -0.18$, $P = 0.02$) and were higher for males (median = 0.65, IQR = 0.49) than females (median = 0.51, IQR = 0.40). In univariate analyses, BCVA in the better and worse eye, and Front Km and TCL in the worse eye were associated with lower VisQol utilities. However, after adjusting for relevant covariates, only BCVA in the better eye remained associated significantly with reduced VisQoL utilities ($\beta = -0.20$, $P = 0.018$).

Conclusions. Using a vision-specific MAUI, our study demonstrated substantial disutility relating to keratoconus. Worse vision in the better eye (but not the worse eye) was associated independently with a reduction in VisQoL utilities, suggesting that considering VisQoL utilities based on vision in the better eye is an important estimate of the impact of keratoconus from the patients' perspective. Treatment and rehabilitation interventions to retard the progression of vision impairment in the better eye resulting from keratoconus would be most efficacious at an early stage to improve QoL outcomes for patients with this disease.

Keywords: keratoconus, quality of life, cross-linking

Keratoconus is a common corneal condition with onset typically during the teenage years and it is characterized by a progressive corneal thinning that results in corneal protrusion, irregular astigmatism and decreased vision.[1] In the early stages, vision is correctable to a large extent with glasses. However, with progression of keratoconus, vision with glasses deteriorates and rigid contact lenses are required. In a minority of patients, the central cornea becomes extremely thin and irregular, and corneal transplantation is required to restore vision.[2,3] Keratoconus is the most common indication for corneal transplantation, accounting for approximately 31% of corneal grafts in Australia.[4]

Despite relatively good visual acuity,[5,6] evidence suggests that keratoconus patients have significantly impaired quality of life (QOL).[7] Daily living activities and emotional well-being have been shown to decrease with increasing severity of keratoconus.[8] Evidence suggests that the significant impact on emotional well-being may be attributed to the increased stress and anxiety of keratoconus patients, even in the early disease stages, relating to concerns over disease progression and the potential need for penetrating keratoplasty.[8] Decreases in visual acuity (VA) and corneal steepening resulting from keratoconus are associated with decreases in vision-related QOL.[8] Recently, Labiris et al.[9] reported that corneal collagen crosslinking (CXL) and CXL combined with topography-guided photorefractive keratectomy may improve self-reported QOL. In keratoconus, large between-eye differences have been found in VA, keratometry, and refractive error between the "better" and "worse" eyes.[10] However, most studies only consider best corrected VA in the better eye or binocular VA when evaluating QOL impact.[11] To date, to our knowledge no studies have examined the association between disease indicators in the worse eye and vision-related QOL in patients with keratoconus.

Previous studies exploring the impact of keratoconus on QOL have used questionnaires, such as the National Eye Institute Visual Function Questionnaire (NEI-VFQ).[7,8] However, to our knowledge no studies have explored the impact of keratoconus from the patients' perspective using utility measures. Utilities are preferences of a health state by a patient and can be measured by time trade off (TTO), standard gamble (SG), and multi-attribute utility instruments (MAUI). Utilities also can be used for the calculation of quality-adjusted life years for economic evaluation of healthcare interventions. The MAUIs allow the comparison of utilities across different disease states and the values are obtained indirectly through patient ratings of their health status from a multifeatured classification system. One of the most commonly used MAUIs is the European Quality of Life Questionnaire (EQ-5D).[12–15] However, results have been inconsistent in vision research, probably because the EQ-5D does not contain any vision-related content and is likely to lack sensitivity to evaluate the burden of vision loss.[16,17] An alternative to the generic EQ-5D is the Vision and Quality of Life Index (VisQoL), which is a six-item vision-specific MAUI validated specifically for vision-impaired populations.[12,18] It uses a descriptive system that measures six life domains affected by a vision-specific condition. A scoring algorithm based on general population surveys using the TTO method has been developed that is used to transform VisQoL responses into VisQoL utilities.[18,19] The VisQoL has been shown to have excellent psychometric properties and is useful as a condition-specific outcome measure for the evaluation of healthcare interventions for the visually impaired.[18]

As keratoconus is an asymmetric condition, we wished to assess the impact of keratoconus on QoL in the better eye and worse eye, separately QoL, using VisQoL. We assessed as indicators of keratoconus severity the effect of best corrected visual acuity (BCVA), front corneal curvature (front Km), thinnest corneal location (TCL), and spherical equivalent refractive error (SE) in the better eye and the worse eye on VisQoL utilities in patients with keratoconus. These data are crucial, as clinical trials will be needed to evaluate new treatment modalities for keratoconus, such as CXL, against traditional methods of treatment from the patient's perspective and from a cost-effectiveness viewpoint.

Methods

Participants were recruited from public clinics at the Royal Victorian Eye and Ear Hospital (RVEEH), private rooms, optometry clinics, or consenting general public corneal clinics. A patient information sheet, consent form, privacy statement, and patient rights were provided to all individuals participating in the study.

Protocol

Participants were required to complete a study questionnaire, clinical examination and complete details of family history of disease. A blood/saliva sample also was collected. The entire procedure lasted less than an hour. The study protocol was approved by the RVEEH Human Research and Ethics Committee (Project #10/954H). Written informed consent was obtained from each participant after explanation of the nature and possible consequences of the study. This protocol followed the tenets of the Declaration of Helsinki and all privacy requirements were met.

Inclusion and Exclusion Criteria

Individuals with keratoconus of any ethnic background, presenting to clinics or private practices were invited to participate in the study. Keratoconus was diagnosed on the basis of the presence of one or more of the following: an irregular cornea, as determined by distortion of keratometric mires and/or Orbscan/Pentacam images; scissoring of the retinoscopic reflex; and demonstration of at least one biomicroscopic sign, including Vogt's striae, Fleischer's ring, or corneal thinning and scarring typical of keratoconus.

Patients with nonkeratoconus ocular disease in both eyes, such as keratectasia, corneal degeneration, macular disease, and optic nerve disease (e.g., optic neuritis, optic atrophy) were excluded from the study. Patients were eligible for the study if they were aged 18 years or older, English speaking, free of significant hearing and cognitive impairment, and living independently.

Assessment of Keratoconus and Related Parameters

Visual acuity was assessed using a logMAR chart at a distance of 3 meters in normal room lighting. Subjective and objective refraction was performed using a modified version of the Early Treatment of Diabetic Retinopathy Study Protocol (ETDRS).[20] Automated refraction was performed using the Nidek auto refractor AR-20 (Designs for Vision, Melbourne, Australia). Average Front Km and TCL were obtained from Pentacam (Oculus, Wetzlar, Germany) images. Pentacam images and objective refraction could not be recorded on patients who attended examination wearing contact lenses, and also those who had recently undergone corneal surgery. In these cases, subjective refraction values were collected. The SE was calculated from the manifest sphere and half cylinders. The biomicroscope slit-lamp examination was used to assess the integrity of the anterior segment of the eye.

Four indicators of disease status were considered in this study: BCVA, average Front Km, TCL, and SE. We considered these disease parameters separately for the better eye and the worse eye. For each disease indicator, the better eye was determined by comparing the within-eye averages of the indicator. The better eye was defined as the eye with the lower average logMAR BCVA, with the flatter average Front Km values, with the thicker cornea, and with the SE closest to the Plano.

Assessment of VisQoL

The VisQoL is a six-item MAUI that covers six dimensions of self-reported vision-related QOL (Table 1). Each question is preceded by "Does my vision. . ." and each item has a series of ordinal responses ranging from "no effect" to "unable to do" plus a "not applicable" option.[19] The health states defined by the VisQoL responses were translated into VisQoL utilities using an existing algorithm that was developed from surveys of the general population.[18] The scale of the utility index ranges from 0 to 1, where 0 represents death and 1.0 represents perfect health. Health states rated worse than death are represented by negative utility values. The main study outcome was the VisQoL utilities.

Assessment of Other Risk Factors

Patients underwent a comprehensive assessment, including a number of questionnaires on education, smoking, and alcohol consumption, and a range of clinical measures. Key covariates included age (years), sex, ethnicity, duration of keratoconus (years), educational attainment, smoking status (nonsmoker/current smoker/past smoker), and alcohol consumption status (never/current drinker/past drinker).

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Table 1. The Six Items in the VisQoL

Item	Response Options
Likely to injure self	1–Unlikely to 5–Almost certainly
Coping with life demands	1–No effect to 6–Unable
Ability to have friendships	1–Easier to 6–Unable, plus a n/a option
Organizing assistance	1–No difficulty to 6–Unable, plus a n/a option
Difficult to fulfill roles	1–No effect to 6–Unable
Confidence to join activities	1–More confident to 6–Not confident at all

n/a, not applicable.

Statistical Analysis

Patient demographics and clinical characteristics were summarized using mean and SD, or median and interquartile range (IQR) values for data measured on a continuous scale, and counts and percentages for categorical data. Normality of the variables was examined using boxplots, and Kolmogorov-Smirnov and Shapiro-Wilk tests. The descriptive data from the VisQoL questionnaire were converted to utilities using the scoring algorithm provided by the Assessment of Quality of Life group. VisQoL utilities was the dependent variable. Student's *t*-test/ANOVA or Wilcoxon rank sum test/Kruskal-Wallis test was used for the comparison of VisQoL utilities among different groups. The relationship between VisQoL utility values, and the measure of the better eye and the worse eye values related to BCVA, Front Km, TCL, and SE values were assessed using Spearman's rank correlation.

Multivariable linear regression analysis was used to examine the association between VisQoL utilities and keratoconus disease indicators, adjusting for factors found to be significant in univariate analysis. All tests were considered to be statistically significant at a level of $P < 0.05$. All statistical analyses were undertaken using Intercooled Stata version 12.1 (StataCorp, College Station, TX).

Results

A total of 170 patients with keratoconus completed the VisQoL. Patients' median age was 33 (IQR = 18) years (range, 14–75 years) and 58% ($n = 99$) were males (Table 2). Of the patients, 24% ($n = 40$) had keratoconus for more than 10 years. The response rate was 89% after excluding those who did not fit our eligibility criteria. Of VisQoL data, 11% were missing as not all participants were able to complete the questionnaire. Sociodemographic and clinical data are presented in Table 2.

The distribution of VisQoL utilities was slightly skewed (Supplementary Fig. S1). However, we tested the normality of the residuals from the multiple linear regression model (Supplementary Fig. S2) and found that the residuals did not violate the normal distribution assumption.

The median VisQoL utility value was 0.60 (IQR, 0.46; range, 0.02–0.99). Compared to patients who had keratoconus for less than 10 years, those who had the disease for 10 years or more had significantly lower utilities ($P < 0.05$, Table 3). VisQoL utilities were significantly negatively correlated with BCVA in the better eye ($\rho = -0.37$, $P < 0.001$) and worse eye ($\rho = -0.31$, $P < 0.001$, Table 3). The VisQoL utilities decreased significantly with Front Km ($\rho = -0.21$, $P < 0.05$) and correlated positively with TCL in the worse eye ($\rho = 0.22$; $P < 0.05$). Utility values were not significantly associated with SE in the better or worse eye (Table 3).

In multivariate regression models, only worse BCVA in the better eye remained significantly associated with reduced utility values, after adjusting for covariates with $P < 0.05$ (Table 4). Worsening of BCVA in the better eye by 0.1 logMAR (1 line) units resulted in a 0.20 decrease in VisQoL utility values.

Discussion

We investigated the relationship between several parameters of keratoconus severity and VisQoL utilities elicited from a large clinical sample. Using the VisQoL, we found that keratoconus was associated with significant disutility. After adjusting for relevant covariates, we found that worse vision in the better eye (but not the worse eye) was significantly independently associated with reduced utility values. Front Km and TCL, in the worse eye, were significantly associated with VisQoL utilities in univariate analysis, but not in multivariate analysis. This suggests that visual acuity in the better eye is the main factor affecting VRQoL in patients with keratoconus. These results supported the traditional belief that the "better" eye is the most important parameter in clinical and research assessments of QoL impact. Treatment and rehabilitation interventions to retard the progression of vision impairment resulting from keratoconus may improve QoL outcomes for patients with this disease.

As there are no reported data to date on the association between utilities and keratoconus to our knowledge, we are unable to compare our findings directly. However, our results support other studies that have reported a substantial impact on patients' QoL due to keratoconus using other types of outcome measures, such as vision-specific QoL questionnaires.

Table 2. Socio-Demographic and Clinical Characteristics of the Patients

Parameters	*N*	
Categorical variable		%
Sex, male	99	58.2
Ethnicity		
European	124	72.9
Others	46	27.1
Education		
Primary school or below	9	5.3
Secondary school	85	50.0
14 y or more	76	44.7
Smoking		
Current	34	20.0
Past	66	38.8
Nonsmoker	70	41.2
Alcohol consumption		
Current	126	74.1
Past	9	5.3
Never	35	20.6
Interval of KC		
Less than 10 y	130	76.5
10 y or more	40	23.5
Continuous variables		Median (IQR)
Age, y	170	33 (18)
Better eye BCVA	160	0.20 (0.4)
Worse eye BCVA	170	0.50 (0.7)
Better eye SE	107	−1.25 (4.50)
Worse eye SE	109	−5.19 (8.50)
Better eye front Km	140	45.00 (3.85)
Worse eye front Km	141	50.90 (10.20)
Better eye TCL	141	484.0 (75.0)
Worse eye TCL	141	431.0 (86.0)

Table 3. Association Between VisQoL Utility Values, and Sociodemographic and Clinical Variables

Parameters	VisQoL Scores Median (IQR)	*P* Value
Categorical variables		
Sex		
Female	0.51 (0.40)	0.03
Male	0.65 (0.49)	
Ethnicity		
Europeans	0.60 (0.47)	0.99
Others	0.59 (0.43)	
Education		
Primary school or below	0.51 (0.20)	0.18
Secondary school	0.55 (0.47)	
14 y or more	0.65 (0.46)	
Smoking		
Current	0.66 (0.38)	
Past	0.53 (0.35)	0.30
Nonsmoker	0.65 (0.51)	
Alcohol consumption		
Current	0.59 (0.44)	
Past	0.60 (0.39)	0.21
Never	0.70 (0.51)	
Duration of keratoconus		
Less than 10 y	0.61 (0.47)	0.03
10 y or more	0.49 (0.41)	
Continuous variables	ρ	*P*
Age	−0.18	0.02
Better eye		
BCVA	−0.37	<0.001
SE	0.07	0.45
Front Km	−0.02	0.81
TCL	0.13	0.12
Worse eye		
BCVA	−0.31	<0.001
SE	0.19	0.05
Front Km	−0.21	0.01
TCL	0.22	0.01

ρ, Spearman's rank correlation coefficient. Univariate analysis.

The Collaborative Longitudinal Evaluation of Keratoconus Study (CLEK) found that people with keratoconus reported significantly impaired VRQoL, as measured by the NEI-VFQ, similar to those with severe age-related macular degeneration (AMD).[7,8] Our findings contrast with a recently published paper by Gothwal et al.[21] who found little impact of keratoconus on vision-specific functioning and emotional well-being using the Impact of Vision Impairment Questionnaire validated using Rasch analysis.[21] Interestingly, mean VisQoL utility values are much lower in our keratoconus subjects compared to patients with diabetic retinopathy (DR; median [IQR] 0.99 [0.00]) for any DR and 0.95 (0.15) for vision-threatening DR.[16] The relatively low VisQoL utility values in persons with keratoconus could be due to their younger age (median = 33 years) compared to people with DR (median = 65 year). Unlike other common chronic ocular morbidities, such as DR and AMD, keratoconus primarily affects people in their teens and early adulthood. The chronic and progressive nature of the disease combined with its early onset may explain the greater disutility reported in this group. Also the frequent changes in spectacle and contact lens prescription with the changes in corneal curvature may impact the ability and efficiency of the patients.

We found that variation in VisQoL utilities was associated with BCVA in the better eye, but not with other indicators of severity of keratoconus, such as Front Km, TCL, and SE. Our findings differ somewhat from other studies. For example, Jones-Jordan et al.[22] showed that using NEI-VFQ, decreases in VA and corneal steepening in the better eye were associated with decreasing VRQoL. In addition, this study reported an association between increasing ocular asymmetry and worse VRQoL; however, in our study we did not find an association with disease asymmetry (data not shown). Also Kymes et al.[8] and Jones-Jordan et al.[22] showed an association of QoL with corneal curvature, while in our study the association was noticed before adjusting for the covariates and not after adjusting. This could be due to the small number of patients compared to the other two studies. However, we feel our results are justifiable due to the fact that Km values may not reflect the BCVA; that is, a person could have steep Ks but 6/6 VA with contact lenses, so their QoL would be good. So, we would think that QoL may not necessarily be directly related to corneal curvature.

Our study suggests that BCVA in the better eye is the most important factor contributing to patient's VRQoL. Considering that keratoconus is largely asymmetric, treatment of the better eye is equally important as treating the worse eye from the patient's perspective. Perhaps this is not surprising as the patient relies more on the better eye for vision and any impact on this eye might have a more pronounced effect on overall wellbeing. This finding has considerable implications for treatment decisions, as clinicians may need to consider basing treatment decisions on the better eye rather than the worse eye, as the latter is unlikely to reflect patient's preferences. Our data suggested that maintaining good vision in the better eye and arresting the progression of keratoconus are essential to reduce the impact of the disease on patients' QoL. It is true that diagnosis of keratoconus in early life is common, but it was found that with CLEK patients, aggressive treatment was postponed until later in life when the keratoconus severity worsens.[23] However, the current data indicated that early detection and management of keratoconus is essential to avoid significant visual loss, which impacts substantially on the QoL of these patients. It is possible that those individuals with severe visual impairment in the worse eye also may impact on VisQoL. Our data were quantitative and we did not explore this aspect, but would be an area of further exploration in keratoconus.

Our finding also reminds the clinicians not to "forget/ignore" the good eye – often clinicians focus on the worse eye, particularly if this eye has been grafted. Also, if a patient has one good eye (such as 6/6) and if the other eye is much worse (such as counting fingers), there perhaps is a dilemma whether

Table 4. Association Between VisQoL Utilities and Disease Indicators of Keratoconus Severity

	β	95% Confidence Interval	*P*
Better eye			
BCVA	−0.20	−0.37, −0.04	0.018
Front Km	0.005	−0.006, 0.016	0.371
TCL	0.001	−0.001, 0.001	0.178
Worse eye			
BCVA	−0.079	−0.184, 0.024	0.131
Front Km	−0.001	−0.010, 0.009	0.859
TCL	0.001	−0.001, 0.001	0.296

* Adjusted for age, sex, and duration of keratoconus. Multivariate analysis.

or not to undertake corneal grafting, wherein the grafted eye would unlikely achieve the same level of VA (as a 6/6) ungrafted eye. Our results that QoL depends on the better eye clearly raise a question if the patient would benefit from the surgery on the worse eye. It is, thus, a reminder for the clinician to make sure they have optimized the good eye, whether or not it has progressive disease, for example, and providing appropriate referral to a contact lens practitioner. The current data also are now extremely relevant to the field of research on keratoconus where novel therapies are emerging. Therapies, such as corneal crosslinking, will need to be compared in terms of clinical and patient-preferred outcomes with traditional treatments. Similarly, health care decision-makers will need to evaluate the cost-effectiveness of these new treatments through the estimation of quality- and disability-adjusted life years as calculated from utilities.

Strengths of the present study include a large clinical sample of keratoconus patients, the comprehensive range of parameters included in the analysis and the use of a vision-specific utility measure. Potential limitations include the higher proportion of men than women in the current sample; however, the results remained significant even after adjusting for sex. Future studies with larger cohorts of keratoconus patients and longitudinal examinations of the changes in VRQoL are needed to confirm the findings in this study.

In conclusion, we found that variation in VisQoL utilities could be attributed to worsening of vision in the better eye (but not the worse eye) of keratoconus patients. To our knowledge, this is the first study to provide data on the impact of keratoconus on patients' QoL using a utility measure. Our findings suggested that clinicians should consider basing treatment decisions on the better eye rather than the worse eye to reflect patient's preferences. Avoiding significant visual loss through early treatment for keratoconus is essential to reduce the QoL impact on patients. Our data are crucial for determining the cost-effectiveness of novel treatments for keratoconus through the estimation of quality- and disability-adjusted life years calculated from utilities. Therapies, such as corneal cross linking, may be essential to arrest the progression of keratoconus and avoid significant impact on QoL.

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