Differential Impact of Unilateral and Bilateral Classifications of Diabetic Retinopathy and Diabetic Macular Edema on Vision-Related Quality of Life

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Purpose. To evaluate and compare the impact of unilateral better-eye and bilateral categorizations of diabetic retinopathy (DR) and diabetic macular edema (DME) on vision-related quality of life (VRQoL) in individuals with type 2 diabetes (T2DM).

Methods. We recruited 390 subjects (116 females; age range, 22–78 years) of Malay, Indian, and Chinese ethnicities from the Singapore Diabetes Management Project (S-DMP), a cross-sectional clinic-based study conducted from 2010 to 2013. Diabetic retinopathy and DME were graded using the Modified Airlie House and American Academy of Ophthalmology classification systems, respectively. Subjects were categorized, using unilateral better-eye classifications, into no DR ($n = 189$), any DR only ($n = 164$), and any DME ($n = 37$); and with bilateral classifications into no DR ($n = 144$), DR/DME in one eye only ($n = 45$), DR in one eye and DR/DME in the other ($n = 164$), and DME in both eyes ($n = 37$). Vision-related quality of life was assessed using the composite Rasch-transformed score of the Impact of Visual Impairment (IVI) questionnaire.

Results. For unilateral better-eye classifications, multivariable linear models revealed a 9% reduction in VRQoL for any DR (β [95% confidence interval (CI)], −0.44 [−0.86, −0.03]) and a 17% reduction for any DME (−0.81 [−1.53, −0.08]) compared to individuals with no DR/DME. Bilateral categorizations revealed significant decrements in VRQoL that occurred only when both eyes had either DR or DME (11%), which worsened when both eyes were affected by DME (22%).

Conclusions. Our results suggest that interventions to prevent the onset of DR and/or DME in the second eye are strongly recommended to significantly reduce the bilateral impact of these conditions on VRQoL.

Keywords: diabetic retinopathy, diabetic macular edema, quality of life, vision impairment

Diabetic retinopathy (DR) is the most common visual complication of diabetes, affecting over half of individuals with a diabetes duration of 20 years or greater.[1] Diabetic macular edema (DME), which can occur at any stage of DR, affects an individual's central vision and is the leading cause of vision loss and blindness in individuals with diabetes.[1,2] The substantial vision loss associated with DR and DME, particularly as these conditions progress to vision-threatening stages, is well documented, as is their debilitating impact on all aspects of a patient's quality of life (QoL).[3,4]

Importantly, most research that assessed the impact of DR and DME on vision-related QoL (VRQoL) have used either the better,[5] or worse affected eye.[6–9] This is problematic because, although it generally is assumed that the better eye is the predominant determinant of overall visual function,[10] this assumption does not account for the considerable loss of stereopsis,[11] visual fields,[12] and anxiety consequent to having only one seeing eye. Some VRQoL studies on bilateral visual impairment (VI) have demonstrated worsening VRQoL as vision deteriorates in the worse eye despite stable vision in the better eye.[13,14] In addition, there is evidence that persons with bilateral DR experience a greater reduction in health-related QoL compared to individuals with unilateral DR.[15] To date, however, we do not have an adequate understanding of how presence or absence of DR and DME in both eyes affects VRQoL. This information may have significant implications for DR and DME management, for instance, in terms of management modality (i.e., active preventative intervention over passive monitoring for those with DR or DME in only one eye) and prioritization (e.g., prioritizing treatment for those with DR or DME in both eyes over those with DR or DME in only one eye).

Therefore, in this study, we examined the impact of unilateral (using the better eye) and bilateral categorizations of DR and DME on VRQoL, assessed using the 28-item Impact of Visual Impairment (IVI) questionnaire,[16] in a clinical sample of

Asian individuals with type 2 diabetes mellitus (T2DM). We hypothesize that our understanding of the impact of DR and DME on VRQoL and the implications of the findings will differ according to whether unilateral or bilateral classifications of DR/DME are used.

Methods

Study Population

The Singapore Diabetes Management Project (S-DMP) is a clinic-based cross-sectional study investigating the clinical, behavioral, and environmental barriers associated with optimal diabetes care in individuals with diabetes with and without DR. The methodology has been described previously.[17] In brief, we recruited 498 individuals with T1DM and T2DM, aged $\geq$ 21 years, from the Singapore National Eye Centre from 2010 to 2013. All participants were free from cognitive impairment (assessed using the 6-item cognitive impairment test),[18] had sufficient hearing to be able to conduct normal conversations, and lived independently in the community (i.e., not living in assisted care facilities). Presence of diabetes was defined as physician-diagnosed diabetes, and with the information retrieved from participants' case notes. Written informed consent was obtained from all participants and the study was approved by the Singapore Centralized Institutional Review Board (Reference, 2010/470/A) and adhered to the tenets of the Declaration of Helsinki. For this study, we excluded participants with T1DM ($n = 10$) and those with missing data ($n = 66$), leaving 422 participants available for further analysis.

Vision-Related Quality of Life (VRQoL)

Vision-related QoL was assessed using the 28-item IVI questionnaire. Designed to assess participation in daily activities and determine the outcome of low-vision rehabilitation on quality of life in persons with low vision,[19] the IVI consists of a composite score and also comprises three subscales, namely Reading and Accessing Information, Mobility and Independence, and Emotional Well-being.[16,19,20] The IVI has undergone substantial psychometric validation using classical and modern psychometric methods[16] and has consistently been shown to be valid and reliable in clinical and population-based samples.[20–24] It also is recommended for use by the American Academy of Ophthalmology and the International Consortium for Health Outcomes Measurement (ICHOM).[25]

Psychometric Assessment of the IVI

Rasch analysis was undertaken to assess the psychometric properties of the IVI in the current sample using the Andrich rating scale model[26] with Winsteps software (version 3.91.2, Chicago, IL, USA). Rasch analysis is a form of Item Response Theory where ordinal raw questionnaire scores are transformed to estimates of interval measures (expressed in log of the odds units, or logits) that demonstrate the essential features of measurement, thus allowing subsequent parametric analyses to be performed.[27] Rasch analysis also provides extensive insight into the psychometric properties of the scale, including response category functioning, measurement precision, item "fit" to the underlying construct (e.g., visual functioning), unidimensionality (i.e., measurement of a single construct), targeting of item difficulty to subjects' ability, and differential item functioning (DIF)/item bias. Rasch analysis is important in clinical research as it increases measurement precision and accuracy, and increases likelihood of detecting significant associations between variables of interest.[27–29]

During Rasch analysis, coding of the IVI was reversed so that a higher score indicated better VRQoL and vice versa. Due to disordered thresholds, response categories were collapsed from 4 to 3. However, the IVI still displayed suboptimal fit to the Rasch model with poor targeting (4.58 logits difference between person and item means), one misfitting item, DIF for sex (six items), and 32 misfitting person measures, although there was no evidence of multidimensionality. The seven items that displayed misfit or DIF were iteratively deleted with no significant loss in fit statistics. To ensure precision, the 32 misfitting person measures also were removed as they contributed significant "noise" and degraded measurement accuracy. Despite these measures, the person separation index (PSI) and person reliability (PR) remained suboptimal ($<$2.0 and $<$0.8, respectively), likely due to the large number of persons without any DR as evident from the poor targeting, indicating a very able population. As such, we also calculated a sample-independent PR coefficient using the person measure standard error generated during Rasch analysis to manually compute the number of statistically different levels of performance that can be identified.[30] We found six statistically distinct levels of performance, and using the formula $6^2/(1 + 6^2)$, a reliability of at least 0.97 was obtained. An IVI composite score for each individual was generated from the Rasch model and used in statistical analyses.

Assessment of DR and DME

Presence and severity of DR was graded from 2-field fundus photographs (Canon CR6 – 45NM; Canon, Inc., Tokyo, Japan) using the modified Airlie House classification system into none (Early Treatment of Diabetic Retinopathy Study [ETDRS] levels 10–15), mild nonproliferative DR (NPDR; level 20), moderate NPDR (levels 31–43), severe NPDR (levels 53–60), and proliferative DR (levels 61–80).

Diabetic macular edema was defined using the classification system by the American Academy of Ophthalmology[31] as hard exudates in the presence of microaneurysms and blot hemorrhage within 1 disc diameter from the foveal center or the presence of focal photocoagulation scars in the macular area. These were confirmed with central macular thickness (CMT) measurements using optical coherence tomography (OCT; Cirrus Version 3.0; Carl Zeiss Meditec, Jena, Germany) using the macular thickness cube scan protocol (512 $\times$ 128). Only scans with signal strength $\geq$ 6 were included.

To quantify the impact of DR and DME presence on VRQoL, DR and DME were unilaterally classified as none, any DR (ETDRS levels $>$ 15 and absence of DME), and any DME (ETDRS levels $>$ 15 with presence of DME) using data from the better eye; and bilaterally categorized as no DR in both eyes, DR in one eye only, DME in one eye only, DR only in both eyes, DR in one eye and DME in the other, and DME in both eyes. Due to the small number of persons with no DR in one eye and DME in the other ($n = 3$), and DR in one eye and DME in the other ($n = 29$), we collapsed these categories, leaving 4 categories of bilateral DR and DME classifications for analysis: no DR in both eyes, DR or DME in one eye only, DR in one eye and DR or DME in the other, and DME in both eyes.

Assessment of Covariates

Information on participants' demographic and socioeconomic characteristics (e.g., age, sex, income, education), lifestyle factors (e.g., smoking), and medical history (e.g., duration of diabetes) was collected using a standardized interviewer-administered questionnaire. Participants were given the choice to be interviewed in English, Mandarin, Malay, or Tamil. Ethnicities were defined by the Singapore census and as

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indicated on the National Registration Identity Card. Clinical covariates were obtained via a standardized clinical examination. Presenting and pinhole distance visual acuity (VA) was checked monocularly with participants wearing current refractive correction (if any) using a logMAR number chart at a distance of 4 m under standard lighting by a trained research officer. Presenting visual impairment was defined as having a VA < 0.3 on the logMAR chart after pinhole refraction. Height was measured in centimeters using a wall-mounted measuring tape and weight in kilograms using a digital scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Trained personnel performed blood pressure measurements using a digital blood pressure machine (Dinamap Pro 100 V2; GE Heathcare, Buckinghamshire, United Kingdom).

Presence of age-related macular degeneration (AMD) was graded from retinal photographs according to the Wisconsin age-related maculopathy grading system,[32] while cataract was graded using slit-lamp biomicroscopy and the lens opacity classification system 3 (LOCS3). Nonfasting venous blood samples also were collected to assess hemoglobin A1c (HbA1c), serum creatinine, serum total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides. All samples were analyzed at the Singapore General Hospital Hematology Laboratory. Hemoglobin A1c was assessed via immunoassay conducted using the Roche Cobas c501 (Roche Diagnostics Ltd, Risch-Rotkreutz, Switzerland),[33] while serum creatinine was assessed using the Roche Integra 800 colorimetric assay (Roche Diagnostics Ltd) calibrated according to the standards set by the National Institute of Standards and Technology (NIST). Likewise, serum total cholesterol, HDL, LDL, and triglycerides were assessed via spectrophotometry conducted using the Beckman Coulter Unicel DxC 800 (Beckman Coulter, Inc., Brea, CA, USA). Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg or a diastolic BP of $\geq$ 90 mm Hg and/or self-reported history; and hyperlipidemia as a total cholesterol level of at least 239 mg/dL (to convert cholesterol level to millimoles per liter, multiply by 0.0259) and/or self-reported history.

Statistical Analysis

All analyses were done using intercooled Stata version 12.1 for Windows (Statacorp, Lake Station, TX, USA). Participant characteristics were first summarized using median (interquartile range [IQR]) or basic proportions for continuous and categorical variables, respectively. Linear regression models were then used to assess the unadjusted associations between participant characteristics, including unilateral and bilateral DR and DME presence and IVI composite score. Finally, multiple linear regression models were used to determine the independent impact of unilateral and bilateral DR and DME presence on the IVI composite score, adjusted for variables found to be significantly associated in unadjusted analyses, as well as variables previously found to be associated with VRQoL in people with diabetes.[5–9,34] Variables included in the models were age, sex, ethnicity, HbA1c, duration of diabetes, education ($\leq$6/>6 years), presence of presenting visual impairment in the better eye, presence of AMD and cataract, and presence of hypertension and hyperlipidemia.

Results

A total of 390 individuals with diabetes was included in the final analysis. A summary of patient clinical and demographic characteristics is described in Table 1. The median (IQR) age of the sample was 58 (53–62) years and 116 (29.7%) were female. The median (IQR) IVI total score was 5.26 (3.36–6.66) logits and 201 (51.5%) had DR or DME in at least one eye. Table 1 summarizes the participant breakdown and potential overlap when using unilateral versus bilateral DR and DME classifications. When individuals with DR and DME were categorized unilaterally using the better eye, 189, 164, and 37 had no DR, any DR, and any DME, respectively. Using bilateral classifications, 144 individuals had no DR or DME in both eyes, 45 had DR or DME in one eye only, 164 had DR in one eye and DR or DME in the other, and 37 had DME in both eyes. In terms of potential overlap, participants categorized as having no DR using unilateral better-eye classifications were further sorted as having no DR in both eyes and DR or DME in only one eye using bilateral classifications. In contrast, any DR and any DME using unilateral better-eye classifications corresponded entirely with DR in one eye/DR or DME in the other, and DME in both eyes, respectively, using bilateral classifications.

Table 1. Matrix Table Showing Breakdown and Overlap in Participants With DR and DME Using Unilateral Better-Eye and Bilateral Classifications

Parameters	No DR, $n = 189$	Any DR, $n = 164$	Any DME, $n = 37$
No DR/no DR	144	0	0
No DR/DR or DME	45	0	0
DR/DR or DME	0	164	0
DME/DME	0	0	37

For unilateral classifications (Table 2), unadjusted models revealed that individuals with any DR only in the better eye had a 10% decrease in VRQoL (regression coefficient [β], −0.48; 95% CI, −0.90 to −0.06), compared to those with no DR. Similarly, having any DME in the better eye was associated with an even greater decrement in VRQoL (20%) compared to no DR (β, −0.97; 95% CI, −1.67 to −0.27). The decline in VRQoL was significantly greater for any DME compared to any DR only (P trend = 0.002). These associations remained significant after multivariable adjustments for confounders, including VI, (9% and 17% relative reduction in VRQoL for individuals with any DR only and any DME in the better eye, respectively, compared to those with no DR; Table 3).

When bilateral classifications were used, unadjusted analyses (Table 2) demonstrated a significant 12% decrease in VRQoL for persons with DR in one eye and DR or DME in the other (β, −0.58; 95% CI, −1.02 to −0.14), compared to having no DR in both eyes. Having DME in both eyes was associated with an even greater loss of VRQoL (24%) compared to having no DR in both eyes (β, −1.22; 95% CI, −1.92 to −0.51, P trend <0.001). These associations remained after multivariable adjustments (11% and 22% relative decrease in VRQoL compared to no DR in both eyes, for DR in one eye and DR or DME in the other, and DME in both eyes, respectively; Table 3). Importantly, VRQoL in individuals with DR or DME in only one eye was comparable to individuals with no DR in both eyes (β, −0.27; 95% CI, −0.94–0.38; $P = 0.4$) in unadjusted models (Table 2), a result that remained unchanged even after multivariable adjustments ($P = 0.3$; Table 3).

Discussion

In this study, we showed that VRQoL systematically worsened in individuals with any DR and any DME, categorized using the better eye. However, although similar results were observed using bilateral classifications of DR/DME, specifically when individuals had DR or DME in both eyes, we found that those

Table 2. Summary of Patient Characteristics and Unadjusted Associations With IVI Total Score

Parameters	Median (IQR)	Regression Coefficient (95% CI)*	*P* Value
Age	58 (53–62)	**0.03 (0.013 to 0.06)**	**0.002**
HbA1c, %	7.4 (6.7–8.5)	−0.012 (−0.14 to 0.11)	0.8
BMI, kg/m^2	25.7 (23.3–28.8)	−0.001 (−0.05 to 0.04)	0.9
Duration of diabetes, y	11.5 (5–20)	**−0.02 (−0.04 to 0.002)**	**0.029**
	N (%)		
Sex, %			
Female	29.7	**−0.48 (−0.91 to −0.04)**	**0.03**
Ethnicity, %			
Chinese	75.6	4.78 ± 0.11	–
Malay	8.21	**−1.05 (−1.82 to −0.28)**	**0.007**
Indians	16.2	−0.52 (−1.06 to 0.018)	0.058
Income, SGD			
≥$2000	64.0	0.005 (−0.28 to 0.29)	0.9
Smoker			
Yes	10.3	0.08 (−0.21 to 0.38)	0.6
Education, y			
≥6	72.2	−0.14 (−0.43 to 0.14)	0.3
Presenting visual impairment, %			
Yes	15.4	**−0.66 (−1.21 to −0.11)**	**0.018**
Hypertension, %			
Yes	55.8	−0.17 (−0.57 to 0.23)	0.4
Hyperlipidemia, %			
Yes	51.0	0.05 (−0.34 to 0.45)	0.8
Chronic kidney disease, %			
Yes	18.2	−0.31 (−0.81 to 0.19)	0.2
AMD, %			
Yes	8.5	0.19 (−0.49 to 0.89)	0.6
Cataract, %			
Yes	4.1	−0.69 (−3.16 to 1.78)	0.6
Unilateral DR and DME status			
No DR	48.5	4.89 ± 0.14	–
DR without DME	42.0	**−0.48 (−0.90 to −0.06)**	**0.023**
DR with DME	9.5	**−0.97 (−1.67 to −0.27)**	**0.006**
		P trend = 0.002	
Bilateral DR and DME status			
No DR in both eyes	36.7	4.99 ± 0.16	–
No DR/any DR or DME	11.5	−0.27 (−0.94 to 0.38)	0.41
Any DR/any DR or DME	42.1	**−0.58 (−1.02 to −0.14)**	**0.01**
DME in both eyes	9.7	**−1.22 (−1.92 to −0.51)**	**0.001**
		P trend < 0.001	

Bold numbers indicate statistically significant *P* values at $P < 0.05$.
* Means score ± SE are given for reference categories.

with DR or DME in only one eye had similar VRQoL compared to those with no DR at all. In other words, a pronounced and significant reduction in VRQoL did not occur until both eyes were affected by DR or DME. In addition, we demonstrated that persons with bilateral DME had almost double the VRQoL loss (compared to those with no DR in both eyes) versus those with bilateral DR, but no or only unilateral DME. Our findings suggest that research into the patient-centered impact of DR and DME should account for the contralateral eye. Moreover, clinical and pharmaceutical interventions to prevent the onset of DR and/or DME in the second eye are critically warranted to prevent substantial VRQoL loss.

Previous studies have reported substantial VRQoL deficits associated with DR and DME in individuals with diabetes.[5–9,34] Using unilateral categorizations, our study showed that persons with any DR had consistently worse VRQoL than those without DR, which worsened in those with DME. This worsening is expected given that the primary clinical presentation of DME is a thickened macula due to leakage and build-up of fluid, leading to distorted vision[35] that is immediately noticeable, whereas DR without DME may progress to more severe stages with relatively few symptoms particularly if the macula is spared.[36] In addition, the reduction in VRQoL due to DR and DME was independent of visual impairment, which is in line with research suggesting that aside from VA, DR and DME also affect other aspects of visual performance, such as color discrimination,[37] contrast sensitivity,[38] and visual fields.[39] Our results corroborate those of other studies that have demonstrated independent associations between increased DR severity and reduced VRQoL.[6,40]

To the best of our knowledge, our study is the first to assess and compare the use of unilateral and bilateral categorization of DR and DME and their impact on VRQoL. As described earlier, unilateral categorizations of DR and DME based on the better eye showed an inverse relationship between DR and DME presence with VRQoL. However, when taking the contralateral eye into account, we found that VRQoL was not significantly affected until both eyes had some level of DR or

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Table 3. Multivariable Adjusted Associations Between Unilateral and Bilateral DR and DME Status With IVI Total Score

Parameters	*N*	Regression Coefficients (95 % CI)*	Relative Change %	*P* Value
DR and DME status by better eye				
No DR	189	4.86 ± 0.15	–	–
DR but no DME	164	**−0.44 (−0.86 to −0.03)**	**9.0**	**0.035**
DR and DME	37	**−0.81 (−1.53 to −0.08)**	**16.7**	**0.028**
		P trend = 0.008		
Bilateral DR and DME status				
No DR in both eyes	144	4.99 ± 0.16	–	–
No DR/any DR or DME	45	−0.35 (−1.00 to 0.28)	7.0	0.3
Any DR/any DR or DME	164	**−0.57 (−1.01 to −0.13)**	**11.4**	**0.01**
Any DME in both eyes	37	**−1.08 (−1.81 to −0.35)**	**21.6**	**0.004**
		P trend = 0.001		

Adjusted for age, sex, HbA1c, ethnicity, education, duration of diabetes, hypertension, hyperlipidemia, age-related macular degeneration, cataract, and visual impairment (better eye). Bold numbers indicate statistically significant *P* values at $P < 0.05$.

* Adjusted means scores ± SE are given for reference categories.

DME, in essence meaning that individuals with one eye free of these conditions had VRQoL comparable to those without any DR in both eyes. Our finding contrasted with that of Finger et al.,[13] who found that VRQoL was significantly affected even if only one eye had mild visual impairment, further suggesting that the VRQoL decrease in DR and DME is independent of VA reduction. In addition, a dramatic worsening in VRQoL was noted in persons with bilateral DME (compared to those with no DR in both eyes) versus individuals with bilateral DR but no or only unilateral DME. Our findings have several important clinical and research implications. First, they strongly advocate for aggressive preventative interventions and more frequent monitoring for individuals with diabetes to keep at least one eye free of DR/DME and, hence, prevent or reduce VRQoL loss prevalent in these conditions. Second, our results indicate that future evaluation of patient-reported treatment outcomes and cost-effectiveness analyses for DR and DME should also account for the effect of the contralateral eye.

Strengths of this study include the comprehensive clinical examination and relatively large number of individuals with DR and DME, adjustment for a range of risk factors including visual impairment, and the use of Rasch analysis to optimize the psychometric properties of the IVI and transform ordinal scores to interval level measures. Limitations included the fact that DR was graded using two-field fundus images, which may have led to an underestimation of DR cases. Furthermore, there may be some selection bias, since individuals with missing data were excluded from analyses ($n = 66$; 13.5%). Moreover, we could not stratify DR and DME cases by severity due to lack of data. Lastly, we did not manage to adjust for all possible causes of VRQoL decline, for example, under-corrected refractive error and glaucoma, as these data were not collected. Therefore, caution should be taken when interpreting these results.

In summary, this study demonstrated that accounting for the effect of the contralateral eye in DR and DME provides more nuanced information on VRQoL that may be missed if only unilateral DR and DME categorizations based on the better eye are used. Our findings support aggressive monitoring and preventative interventions for individuals with diabetes to prevent the onset of DR and/or DME in the second eye to maintain satisfactory VRQoL.

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