Singapore has one of the highest rates of diabetes globally

- Approximately 13% of Singaporeans between 20-79 years have diabetes (DM; IDF Diabetes Atlas 2015)
  - Second highest proportion among developed nations
  - Prevalence among three major ethnicities is estimated at 11.5% in Chinese, 17.1% in Malays, 21.6% in Indians ≥ 40 years (Chiang et al, 2011)

- DM prevalence and burden estimated to increase in coming decades due to increasing affluence and longer lifespan
- Projected economic burden of US$2 billion by 2050
Diabetic Eye Diseases

- Diabetic retinopathy (DR) and diabetic macular edema (DME) are among the most common visual complications of diabetes.
- Leading causes of visual impairment (VI) in working-aged adults (Cheung et al. 2010).
- Age-standardized DR prevalence of 35.0%, 30.4% and 26.2% in Malays, Indians, and Chinese, respectively.
- Corresponding DME estimates are 5.7%, 7.2% and 6.1% (SEED Data)
Diabetic Eye Diseases

• Common risk factors: ↑ diabetes duration, ↑ HbA1c levels, ↑ systolic blood pressure, presence of hypertension, stroke and cardiovascular disease

• Almost 80% of those with DR were unaware they had the condition (Huang et al, 2015)

• Important gaps in patients’ knowledge about DR

• Potentially damaging beliefs about the cause of DR and the effect of treatments on vision
DR & DME: Patients’ perspectives

Qualitative work by our group in Australia has highlighted the diverse burden of DR/DME on QoL (Fenwick et al. 2012)

Patient focus group, transcript analysis:

“The effects on me were devastating. I had to leave my job, which was teaching, and my hobby was stamp collecting and I used to write… All my interests, just overnight I was unable to do them. But probably the worst problem for me has been psychological…I had a fair bit to offer my wife, but when I lost my vision I suddenly felt that I had nothing to offer her. So I told her to go so that she didn’t have to put up with a…fat old man who was blind.”

Emotional; Economic; Activity limitation; Convenience; Social
Diabetic Eye Diseases

- DR/DME has a substantial impact on patients’ vision-specific functioning (VSF) and vision-related QoL (VRQoL), particularly at the vision-threatening stages

ABSTRACT
Understanding the impact of a condition from the patient’s perspective is important, and different types of patient-reported outcomes or instruments are available to help with this. This review article summarises the current evidence on the impact of diabetic retinopathy (DR) and its associated vision impairment on patient-reported outcomes. We have included research that has used a range of outcome measures to assess the impact of DR on generic health-related quality of life, utility, vision-functioning and vision-specific quality of life. This review also offers clarification on frequently misused psychometric terminologies to help clinicians and researchers better understand the literature associated with patient-reported outcome research. Overall, the evidence suggests that DR, particularly in its vision-threatening stages, has a substantial, negative impact on the patient. However, our understanding of the impact of DR on HRQoL, a complex concept that encompasses functional ability, symptoms, emotional well-being, social relationships, concerns and convenience as they are affected by vision. However, as other parameters are often used, sometimes mistakenly, to characterise vision-related QoL, we also include studies that have assessed the impact of DR using generic health-related QoL questionnaires, utilities and visual functioning questionnaires. Table 1 summarises the different characteristics of these PROs. This review also offers a critical appraisal of the outcome measures used by researchers to assess QoL and informs the readers about future directions to overcome these limitations, such as the third generational outcome measures item
Impact of DR on utility

- Utilities are expressions of limitations endured as a result of a health problem
- They provide a preference-based single index of utility associated with a health impairment or QoL state (0-1 range; 1=‘perfect’ and 0=death)
- Numerous studies have shown that utilities for DR systematically decrease with worsening visual acuity and DR severity, ranging from 0.98 to 0.53
- Considerable variance in utility values due to type of utility measure, sample size, disease severity and population
The variation in VisQoL utilities was attributed to profound visual impairment (VI), but not mild, moderate or severe VI, or DR severity

The EQ-5D was not sensitive to any level of DR or VI

The Impact Of DR On Utility

Clinical and Epidemiologic Research

The Impact of Diabetic Retinopathy and Diabetic Macular Edema on Health-Related Quality of Life in Type 1 and Type 2 Diabetes

Eva K. Fenuwick, Jing Xie, Julie Randcliffe, Konrad Pesudovs, Robert P. Finger, Tien Y. Wong, Ecosse L. Lamoureux

Purpose: To assess the impact of diabetic retinopathy (DR) and diabetic macular edema (DME) on health-related quality of life (HRQoL) in type 1 and type 2 diabetes using the EuroQol EQ-5D generic multi-attribute utility instrument (MAUI).

Methods: In this cross-sectional study, 577 patients with diabetes were recruited from specialized eye clinics in Melbourne, Australia. Each patient underwent clinical, biochemical, and anthropometric assessments. The severity of combined DR and DME (no DR/DME; mild NPDR [nonproliferative DR (NPDR)] and/or mild DME; moderate NPDR and/or moderate DME; and vision-threatening DR (VTDR) [severe NPDR or PDR and/or severe DME]) in the worse eye was calculated. EQ-5D utility measures were the main outcome. Because the distribution of the utility measures was skewed, independent associations were explored using multivariate quantile regression models (five quantiles, namely 15th, 50th, 65th, 70th, 75th) ranging from poorest to highest HRQoL.

Results: Median age of the participants was 66 years (range, 16-100 years) of the 577 participants, 394 (68.5%) had type 1 diabetes.

Conclusions: Using a generic MAUI, the EQ-5D, the authors found that the presence or severity of DR/DME and comorbid vision loss were not associated with any quantile of HRQoL. These findings suggest that the EQ-5D lacks sensitivity in assessing the impact of the severity of DR/DME on HRQoL parameters and that condition-specific instruments may better capture the full impact of the association. (Invest Ophtalmol Vis Sci. 2012;53:3001-3000. DOI:10.1167/iovs.11-8992)

Diabetic retinopathy (DR) is a common microvascular complication of diabetes. In its early nonproliferative stages there are few visual symptoms; however, as the disease progresses to vision-threatening stages (severe nonproliferative DR [NPDR] and proliferative DR [PDR]), significant vision loss can occur. Diabetic macular edema (DME), which can occur at any stage, affects central visual acuity. After 20 years of living with diabetes, most patients will have some degree of DR. As shown by our group, the impact of DR and associated vision loss on health-related quality of life (HRQoL) is
### Impact Of DR On Utility

- Current work in Australia to develop a utility measure for DR/DME using discrete choice experiments (DCE)

<table>
<thead>
<tr>
<th></th>
<th>Scenario A</th>
<th>Scenario B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual symptoms</td>
<td>Severe difficulty</td>
<td>Some difficulty</td>
</tr>
<tr>
<td>e.g. blur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lighting and glare</td>
<td>Some difficulty</td>
<td>Severe difficulty</td>
</tr>
<tr>
<td>e.g. bright lights</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity limitation and</td>
<td>No difficulty</td>
<td>Some difficulty</td>
</tr>
<tr>
<td>mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g. housework, steps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconvenience</td>
<td>Some difficulty</td>
<td>Severe difficulty</td>
</tr>
<tr>
<td>e.g. needing help</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>Some difficulty</td>
<td>No difficulty</td>
</tr>
<tr>
<td>e.g. feel upset, loss of social life</td>
<td>You live for 1 year in this stage</td>
<td>You live for 5 years in this state</td>
</tr>
</tbody>
</table>

Which scenario would you prefer?
Impact Of DR On VSF (Vision-dependent IADL)

- Activities with most functional decreases are reading small print, mobility, work, and leisure (Lamoureux et. al 2004)

- Those with more severe DR and VA loss consistently report worse VSF compared to those with less severe DR and VA loss (Klein et. al 2001; Cusick et. al 2005)
  - Compared to those with NPDR, those with PDR had scores 20-30 points lower (out of 100) on the NEI-VFQ (Gabrielian et. al 2010)
  - Those with DME have worse VSF than those with DR without DME (Hariprasad et. al 2007)

- However, even relatively mild levels of VA loss place substantial burden on VSF (Lloyd et. al 2008)
Impact Of DR On VSF In Singapore

• 357 participants with diabetes from SiMES answered the VF-11.

• Persons with visual threatening DR (VTDR) and proliferative DR (PDR) were 6 and 12 times more likely to report worse VSF, respectively, independent of visual acuity.

• Interventions to prevent progression to vision-threatening stages are required.

Impact of Diabetic Retinopathy on Vision-Specific Function

Ecosse L. Lamoureux, MSc, PhD,1,2 E. Shyong Tai, MCRP,3 Julian Thumboo, FRCP,4 Ryo Kawasaki, MD, PhD,1 Seang-Mei Saw, MBBS, PhD,2,5 Paul Mitchell, MD, PhD,6 Tien Y. Wong, FRCS, PhD1,2,6,7

Objective: To assess the influence of the spectrum of diabetic retinopathy (DR) on vision-specific function in an Asian population.

Design: Population-based cross-sectional study.

Participants: Persons aged 40 to 80 years of Malay ethnicity in Singapore.

Methods: The Singapore Malay Eye Study was a population-based, cross-sectional study of 3280 Asian Malays (78.7% response rate). Five end points were considered: (1) any DR, (2) macular edema (ME), (3) clinically significant macular edema (CSME), (4) vision-threatening DR (VTDR), and (5) DR severity levels ranging from none to proliferative diabetic retinopathy (PDR). Vision function was assessed using the Vision-Specific Functioning Scale validated using Rasch analysis.

Main Outcome Measures: Vision-specific functioning score.
Impact of DR on social and emotional well-being

- Patients with DR believe they experience more symptoms relating to their diabetes and that diabetes has a greater impact on their life.
  - Negative beliefs about diabetes were associated with higher levels of depression and anxiety.

- Severe DR independently associated with greater depressive symptoms ($\beta=0.69; 95\% \text{ CI } 0.03-1.34$)
  - Explaining 19% of the variance in depression.
Impact Of DR On Social And Emotional Well-being

- Disruption of family functioning, relationships and roles; increased social isolation and dependence; deterioration of work prospects; increased financial strain.
- Fear, anxiety, vulnerability, guilt, loss of confidence, anger, stress and poor self-perception.
Impact of Severity of DR on QoL in Singapore

- We explored the impact of DR on QoL in 292 patients with diabetes in the SCES.
- Impact of Vision Impairment Questionnaire (IVI) assesses Reading and Accessing Information; Mobility and Independence; Emotional well-being.
- Of the 292 participants, 31.2% had any DR; 9.3% had VTDR; and 7.5% had PDR.

<table>
<thead>
<tr>
<th></th>
<th>Reading %</th>
<th>Emotional %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DR</td>
<td>β= -0.46 (CI -0.87, -0.04)</td>
<td>β= -0.50 (CI -0.96, -0.23)</td>
</tr>
<tr>
<td>VTDR</td>
<td>β= -0.65 (CI -1.31, -0.06)</td>
<td>β= -1.14 (CI -1.86, -0.42)</td>
</tr>
<tr>
<td>PDR</td>
<td>β= -0.69 (CI -1.47, -0.01)</td>
<td>β= -1.36 (CI -2.19, -0.53)</td>
</tr>
</tbody>
</table>

Bolded values represent independent variables significantly associated with QoL outcome (p<0.05)
Adjusted for age, gender, stroke, socioeconomic factors (education and income) and presenting VA, and diabetic risk factors (including BMI, HbA1c, duration of DM, chronic kidney disease, hyperlipidemia, and hypertension)
Impact of Severity of DR on VRQoL in Singapore

- Similar findings to the SiMES study which used the VF-11
- Only VTDR and PDR were associated with worse visual functioning when presenting VA was included in the model
- In contrast, we found that Mobility was not associated with DR
  - May suggest that Mobility is a less important construct for Chinese patients than Reading and Emotional
  - Few ‘mobility’ items in the VF-14
Impact of unilateral and bilateral DR on VRQoL

Singapore Diabetes Management Project (S-DMP) was a cross-sectional, clinical study of 390 individuals of Malay, Indian and Chinese ethnicity with diabetes.
Differential Impact Of Unilateral And Bilateral DR On QoL

• Unilateral classification of DR:
  – 9% reduction in VRQoL for any DR (β= -0.44 CI -0.86, -0.03)
  – 17% reduction in VRQoL for any DME (β= -0.81 CI -1.53, -0.08)

• Bilateral classification of DR:
  – 11% reduction in VRQoL for Any DR / any DR or DME (β = -0.57 CI -1.01, -0.13)
  – 22% reduction in VRQoL for any DME in both eyes (β = -1.08 CI -1.81, -0.35)

• Research into the patient-centered impact of DR and DME should account for the contralateral eye.

• Interventions to prevent the onset of DR and/or DME in the second eye are strongly recommended.
More Research Needed?

- Limitations with the existing PROs
  - Most measure 1-3 QoL domains
- Limited number of items
  - Not suitable for population (too easy or too difficult)
- Traditional summative scoring method
  - Well-known psychometric limitations
- Paper and pencil based
  - No real-time data collection & feedback
**Item Banking and CAT**

- **Item bank** – large pool of items (questions) calibrated for difficulty on the same scale using Rasch analysis
- **Computer adaptive testing** – method of administering tests where computer software adapts the item asked depending on a person’s response to previous items
DR/DME Item Banking and CAT Development

Phase 1
• Content development via qualitative interviews

Phase 2
• Item reduction
• Develop pilot item bank

Phase 3
• Pilot test item bank in large patient sample

Phase 4
• Psychometric testing & calibrate items
• Initial CAT testing

Phase 5
• Develop CAT
• Validate item banks via CAT
### Phase 3: Specific item banks and 314 items

<table>
<thead>
<tr>
<th>Quality of life Domains</th>
<th>Number of items</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Activity limitation (AL)</td>
<td>120</td>
</tr>
<tr>
<td>2. Mobility (MB)</td>
<td>19</td>
</tr>
<tr>
<td>3. Visual symptoms (VS)</td>
<td>18</td>
</tr>
<tr>
<td>4. Ocular comfort symptoms (OS)</td>
<td>10</td>
</tr>
<tr>
<td>5. Convenience (CV)</td>
<td>30</td>
</tr>
<tr>
<td>6. Health concerns (HC)</td>
<td>36</td>
</tr>
<tr>
<td>7. Emotional well-being (EM)</td>
<td>48</td>
</tr>
<tr>
<td>8. Social (SC)</td>
<td>21</td>
</tr>
<tr>
<td>9. Economic (EC)</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>314</strong></td>
</tr>
</tbody>
</table>
Phase 4 A: Psychometric Evaluation

Ocular Surface Symptoms had unresolvable psychometric issues.

Activity Limitation & Convenience were modified due to multidimensionality.

→ Two new item pools: Driving and Lighting.

Economic was expanded to include work-related items from Activity Limitation and Mobility.
Phase 4B: CAT Simulations

- CAT simulation: Firestar-D-Software (http://cran.r-project.org/) (n=1000)
  - Estimate number of items required to obtain high and moderate levels of precision – set stopping rules

- Simulation 1: High precision, Standard Error of Measurement (SEM) = 0.387 (reliability = 0.85)

- Simulation 2: Moderate precision, SEM = 0.521 (reliability = 0.72)
Table 2. CAT simulation results for the diabetic retinopathy item banks: high precision

<table>
<thead>
<tr>
<th>Item bank</th>
<th>No. of items available for CAT</th>
<th>Average no. of items used by CAT</th>
<th>Correlation between CAT and item bank theta</th>
<th>Mean SEM (sem.CAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Symptoms</td>
<td>18</td>
<td>7.7</td>
<td>0.97</td>
<td>0.38</td>
</tr>
<tr>
<td>Activity Limitation</td>
<td>92</td>
<td>5.3</td>
<td>0.94</td>
<td>0.37</td>
</tr>
<tr>
<td>Mobility</td>
<td>17</td>
<td>9.1</td>
<td>0.97</td>
<td>0.38</td>
</tr>
<tr>
<td>Emotional</td>
<td>45</td>
<td>6.5</td>
<td>0.94</td>
<td>0.38</td>
</tr>
<tr>
<td>Health Concerns</td>
<td>35</td>
<td>5.8</td>
<td>0.95</td>
<td>0.37</td>
</tr>
<tr>
<td>Social</td>
<td>20</td>
<td>7.1</td>
<td>0.96</td>
<td>0.37</td>
</tr>
<tr>
<td>Convenience</td>
<td>20</td>
<td>6.7</td>
<td>0.96</td>
<td>0.38</td>
</tr>
<tr>
<td>Economic</td>
<td>15</td>
<td>5.9</td>
<td>0.97</td>
<td>0.37</td>
</tr>
<tr>
<td>Driving</td>
<td>15</td>
<td>8.7</td>
<td>0.98</td>
<td>0.38</td>
</tr>
<tr>
<td>Lighting</td>
<td>10</td>
<td>8.1</td>
<td>0.99</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>287</strong></td>
<td><strong>70.8 (24.7%)</strong></td>
<td><strong>0.96</strong></td>
<td><strong>0.38</strong></td>
</tr>
</tbody>
</table>
# Preliminary results 4B

## Table 2. CAT simulation results for the diabetic retinopathy item banks: **moderate precision**

<table>
<thead>
<tr>
<th>Item bank</th>
<th>No. of items available for CAT</th>
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<th>Mean SEM (sem.CAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Symptoms</td>
<td>18</td>
<td>3.3</td>
<td>0.88</td>
<td>0.50</td>
</tr>
<tr>
<td>Activity Limitation</td>
<td>92</td>
<td>3.1</td>
<td>0.88</td>
<td>0.47</td>
</tr>
<tr>
<td>Mobility</td>
<td>17</td>
<td>4.5</td>
<td>0.91</td>
<td>0.50</td>
</tr>
<tr>
<td>Emotional</td>
<td>45</td>
<td>3.3</td>
<td>0.89</td>
<td>0.50</td>
</tr>
<tr>
<td>Health Concerns</td>
<td>35</td>
<td>3.1</td>
<td>0.89</td>
<td>0.48</td>
</tr>
<tr>
<td>Social</td>
<td>20</td>
<td>3.4</td>
<td>0.89</td>
<td>0.49</td>
</tr>
<tr>
<td>Convenience</td>
<td>20</td>
<td>3.3</td>
<td>0.90</td>
<td>0.49</td>
</tr>
<tr>
<td>Economic</td>
<td>15</td>
<td>2.9</td>
<td>0.91</td>
<td>0.48</td>
</tr>
<tr>
<td>Driving</td>
<td>15</td>
<td>3.9</td>
<td>0.91</td>
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<td>Lighting</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>287</strong></td>
<td><strong>34.8 (12.1%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Future Work- Phase 5

- Validation of the 10 item banks using CAT via an online platform with tablet administration
- English and other Languages
  - Completion time
  - Content range coverage and test precision
  - Temporal reliability
  - Criterion, convergent and divergent validity
Summary

- DR has a substantial impact on daily activities and several aspects of VSF and QoL especially, emotional well-being
- However, work in this area could be improved with a DR/DME item bank a more sophisticated, sensitive and comprehensive PRO
- Valuable clinical and research applications
- Timely as new treatments for DR/DME continue to emerge and need evaluation from the patient’s perspective and cost-effectiveness
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