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2. Type of paper –

Study protocol

3. Length of paper –

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4. Title page
Development and Validation of a Diabetic Retinopathy Screening Intervention Using a Hand Held Non-Mydriatic Digital Retinal Camera by Physician Graders at a Tertiary Level Medical Clinic - A Study Protocol

5. Key words

Diabetes, diabetic retinopathy, screening, mydriatic, non mydriatic, digital imaging, Sri Lanka

6. Trial Registration –

Not applicable

7. Abstract -

Introduction -

The risk of visual loss from diabetic retinopathy (DR) can be reduced by early screening and treatment. The Western province of Sri Lanka has the highest prevalence of diabetes mellitus (18.6%) in the country. A situational analysis identified a significant gap in DR screening services uptake in this region. This paper describes the methods of development and validation of a screening intervention using a hand held nonmydriatic digital camera.

Objective -

This study aims to validate a DR screening intervention for the local context.

Methods -

The intervention was developed after assessing barriers and identifying the most appropriate personnel, modality and location for screening services. The study will be conducted in a public sector tertiary care centre in the Western province of Sri Lanka. Two trained physicians will capture non-mydriatic and mydriatic retinal images using a hand held digital retinal
camera (n=506 people with diabetes) and grade images for DR. The validity of the proposed screening intervention will be assessed compared with a reference standard.

Results -

We will analyse the validity of screening by physician graders and calculate sensitivity, specificity and predictive values for each method of screening and by grader.

Conclusion -

The outcome of this study will be useful for implementation of a DR screening program in this region and in similar communities.
8. Main Text -

Introduction -

The prevalence of diabetes and the number affected is increasing rapidly in all regions. An estimated 425 million people had diabetes in 2017 rising to 629 million in 2045. (1) The crude prevalence of diabetes in Sri Lanka was 12.6% (>20 years), being highest in the Western province (18.6%, 95% CI 15.8–21.5%). (2) In Western province there are approximately 750,000 (>18 years) people with diabetes (PwDM), 150,000 (20%) of whom are likely to have non-proliferative DR (NPDR).

Many studies report that visual loss from DR can be largely prevented by early screening and appropriate treatment. (3–5) However, there is no systematic DR screening in Western province where the number screened and treated was far lower than the anticipated need in 2014. (6) The aim of this protocol is to describe the methods of validation of a DR screening intervention using digital imaging.

Methods -

Ethics review committees of National Eye Hospital and London School of Hygiene & Tropical Medicine have granted approval.

Initial formative research showed that non-mydriatic digital retinal imaging at medical clinics by general physicians was a potential option for the local setting. Nine general physicians were selected from a tertiary level institution following informed consent and underwent a competency-based training by two retinologists from a tertiary centre, which included the following: capturing retinal fields using a hand-held fundus camera, identification of signs of DR using images and DR grading according to an adapted classification system (Table 1).
Macular changes are graded as none - M0; exudate/s or blot haemorrhage/s within 2 disc diameters from the centre of the fovea, M1. Guidelines were used to standardize reporting of image quality which included ungradable images based on the proportion of the retina visible to be graded (figure 1). Physicians were tested using a set of standard images of DR and the two who reached the required level of agreement with the retinologist (k=0.8–0.9) were selected as graders in the validation study.

The sample size (n=506) was calculated based on 95% confidence intervals, 10% margin of error, expected sensitivity 70% and prevalence of moderate NPDR among PwDM of 20%. This included an additional 25% to take account of un-gradable images. Interim analysis will be undertaken to ascertain the level of ungradable images (i.e. <50% of the retina visible) and the sample size increased, if required.

A consecutive sample of diagnosed PwDM (>18 years) without previous DR screening at an eye clinic will be eligible to participate, after giving written informed consent. Eligible participants will be recruited by trained research assistants when PwDM present for routine medical care at the main tertiary centre in Colombo. The PwDM with previous retinal screening, DR related treatment (laser treatment, intra-vitreal injections and pars-plana-vitrectomy), and those who were currently under any DR screening program or treatment will be excluded from study.

Two field non-mydriatic and mydriatic retinal images will be captured and stored in the screening test. Participants will undergo digital retinal imaging (using Zeiss-Visuscout100®
fundus camera) by the physician graders at the time of presentation. Firstly, two field (1st field–macula centred, 2nd field-disc centred) (figure 2), 45° retinal images will be captured in each eye by each physician grader without pupillary dilatation. Secondly, participants’ pupils will be dilated using 1% tropicamide and the same fields will be captured, following adequate mydriasis (5-6 mm). During grading, the non-mydriatic images will be graded first. The graders will be masked to the history and clinical examination findings.

The reference test will entail a detailed, dilated fundus examination by an experienced retinologist using slit-lamp bio-microscopy with a 90D lens and indirect ophthalmoscopy using a 20D lens. This examination will take place as soon after imaging as possible. The retinologist will be masked to the clinical status and physician graders’ findings.

For quality assurance 15% of each non-mydriatic and mydriatic image sets will be evaluated by the retinologist for technique, ability to image the required field and gradability. Fifteen percent of each hundred image sets will be given back to the physician graders for double grading to assess the repeatability and intra-grader agreement in 1st attempt and 2nd attempt of grading images. A sample of the same images sets (n=200) will be graded by the retinologist to calculate inter-grader agreement.

We will analyse the validity of screening by physician graders and calculate sensitivity, specificity and predictive values with 95% confidence intervals for each method of screening and by grader. Intra and inter-grader agreement for both mydriatic and non-mydriatic index tests will be calculated and compared to the findings by the retinologist. Subgroup analysis
will be conducted for identification of presence/absence of DR (any DR), moderate NPDR and above with / without macular signs, to make recommendations for a referable criterion for the local context.

**Results -**

The results of this study will be published in detail elsewhere according to the Quality Assessment of Diagnostic Accuracy Study guidelines (QUADAS-2). (7) Data will be entered into MS Excel (2016) worksheet and transferred into STATA/IC-v14.2 (2015-USA) analytical package following cleaning, consistency checks and analysis. The sensitivity, specificity and predictive values for each strategy and each level of DR will be presented using average of the same variables of two physician graders (non-mydriatic and mydriatic separately) compared to the reference standard. This will be presented with 95% confidence intervals.

**Discussion -**

We have described the methods of training and validation of a digital retinal imaging technique which can be adapted in LMICs. To our knowledge this will be the first study of this kind in Sri Lanka. The level of skills acquired by the physician graders is an important factor in the screening outcome. Different non-ophthalmologist graders have conducted DR screening successfully.(8–10) In addition, we will be able to study the effect of a range of population characteristics on the validity of detecting DR using imaging and to understand the role of non-ophthalmic personnel in order to make recommendations for a systematic DR screening program in Western province.

**Conclusion -**
The outcome of this study will be useful for implementation of a DR screening program in this region and in similar communities.
9. References -


Table 1 – Adapted diabetic retinopathy classification for the validation study -

<table>
<thead>
<tr>
<th>Signs</th>
<th>No DR (R0)</th>
<th>Mild BDR / NPDR (R1)</th>
<th>Moderate BDR / NPDR (R2)</th>
<th>Severe NPDR (R3)</th>
<th>Proliferative DR (PDR) (R4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microaneurysms</td>
<td>No</td>
<td>Few</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Present</td>
</tr>
<tr>
<td>Hard Exudates *</td>
<td>No</td>
<td>Few</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Present</td>
</tr>
<tr>
<td>Cotton wool spots</td>
<td>No</td>
<td>Occasional</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Present</td>
</tr>
<tr>
<td>Intra retinal haemorrhage*</td>
<td>No</td>
<td>Few</td>
<td>&gt;20 in 1-3 quadrants</td>
<td>&gt;20 in 4 quadrants</td>
<td>Present</td>
</tr>
<tr>
<td>Venous beading</td>
<td>No</td>
<td>Occasional</td>
<td>Present in 1-2 quadrants</td>
<td>Present in &gt;2 quadrants</td>
<td>Present</td>
</tr>
<tr>
<td>IRMA+</td>
<td>No</td>
<td>No</td>
<td>Present ~1 quadrant</td>
<td>Prominent &gt;1 quadrant</td>
<td>Present</td>
</tr>
<tr>
<td>NVD ^</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present</td>
</tr>
<tr>
<td>NVE ^</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present</td>
</tr>
<tr>
<td>Vitreous / pre retinal haemorrhage</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present - advanced PDR</td>
</tr>
<tr>
<td>Traction</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present - advanced PDR</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Present - advanced PDR</td>
</tr>
</tbody>
</table>

*Not within the definition of maculopathy.

+Intra retinal microvascular abnormalities

^ Neo-vascularisations over the disc / elsewhere
Figure 1 – Evaluation of image quality – levels of gradability based on the proportion of the image which can be graded

<table>
<thead>
<tr>
<th>Gradable</th>
<th>Ungradable</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% Gradable</td>
<td>75% Gradable</td>
</tr>
<tr>
<td>50% Gradable</td>
<td>&lt;50% Visible</td>
</tr>
</tbody>
</table>

Figure 2 - Two retinal images captured
<table>
<thead>
<tr>
<th>Field 1 Centred on the macula</th>
<th>Field 2. Centred on the optic disc</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Field 1" /></td>
<td><img src="image2.png" alt="Field 2" /></td>
</tr>
</tbody>
</table>

*Colour prints cost - borne by author, LKR 7,500*
11. Sources of Support -

A research degree student project grant from Queen Elizabeth Diamond Jubilee Trust – United Kingdom, coordinated through Commonwealth Eye Consortium – UK.

12. Authors’ Contribution –

Dr. P.N. Piyasena is coordinating and conducting this research project in the Western province as a fulfilment of a research degree. Prof. G.V.S. Murthy and Dr. J.Y.L. Yip supervised the student work.

Dr. P.N. Piyasena, Prof. G.V.S. Murthy, Prof. C. Gilbert, Associate Prof. J.L. Yip, Prof. T. Peto and Mr. D. MacLeod made substantial contributions for the concept development, methodology and study design. Dr. C. Fonseka is the principal investigator of the project from collaborating institution and supervised the project work locally. Dr. A. Kulatunga will supervise the project related work of diabetic retinopathy screening at medical unit.

Dr. M. Dhanapala and Dr. K. Banduthilaka conducted the training of physician graders and Dr. K. Banduthilaka will conduct the reference standard clinical examination of the participants. Dr. M. Dhanapala and Dr. K. Banduthilaka will involve in managing the study participants those who require further investigations and treatment. Dr. L. Pathirana and Dr. H. Dassanayaka will conduct the validation of diabetic retinopathy screening intervention at present in the Western province.

All authors contributed in preparation the manuscript, read and approved the final manuscript to publish in the JMIR.
13. Acknowledgements

Investigators thank Association of Vitreo Retina Specialists of Sri Lanka for the logistical and operational support provided in conducting this study.

14. Conflict of interest

None declared

15. Abbreviations

DR-diabetic retinopathy

D-dioptres

LMIC-Lower middle income country

NPDR-Non proliferative diabetic retinopathy

PwDM-People with diabetes mellitus

QUADAS-Quality assessment tool for diagnostic accuracy studies