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The muranga teleophthalmology study: comparison of virtual (teleglaucoma) with in-person clinical assessment to diagnose glaucoma

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INTRODUCTION

There are 60 million people with glaucomatous optic neuropathy resulting in 8.4 million cases of blindness from glaucoma world-wide. The burden of glaucoma is expected to increase significantly with an estimated 80 million people with glaucomatous optic neuropathy and 11.2 million blind by 2020. Epidemiology studies world-wide suggest that primary open
angle glaucoma (POAG) disproportionately affects Africans, and this population accounts for the highest prevalence of all POAG cases.\(^2\) POAG in Africans may present at an earlier age, is associated with higher intraocular pressure (IOP), progresses more rapidly, and presents in late stages.\(^2,4\) Furthermore, cases of glaucoma in African populations present with increased severity and are more difficult to treat.\(^5\)–\(^7\) In East, Central and Southern Africa, glaucoma affects an estimated 10,000 people per million and approximately 400 new cases of glaucoma per million are diagnosed yearly.\(^1\)

Due to a limited number of trained health-care workers and limited diagnostic equipment, early diagnosis and follow-up treatment are especially challenging in many parts of Africa. Hence, innovation is required to optimally utilize the limited funding and other finite resources to address the burden of glaucoma and its related increase in morbidity.

Telemedicine refers to the evaluation and treatment of disease of patients at a distance. Teleophthalmology narrows the scope to eye diseases detected and managed from a distance. Teleglaucoma (TG), refers to the evaluation and treatment of glaucoma among patients at a distance.\(^8\) A TG program requires telemedical technologies that can provide two or three dimensional images of the nerve and online tools to grade glaucomatous cupping of the optic disc.\(^9\) With TG, ophthalmologists can evaluate stereo images sent via the internet using the prismatic viewers, red-green anaglyph spectacles or liquid crystal display shutter glasses.\(^9\) Although the majority of teleophthalmology to date has been on teleretinal applications, programs can and should be established to diagnose glaucomatous optic nerve disease for timely treatment.

A study from South Africa demonstrated that TG was a cost-effective international development project. The connection to ophthalmologists from donor countries allowed South African practitioners to learn new procedures, improving ophthalmic clinical practice.\(^10\) TG has the potential to strengthen the capacity in the drive to build health-care infrastructure.\(^10\) The advantage lies in the potential to provide rural populations that have limited access to ophthalmic care, with better care through early diagnosis and prevention of vision related morbidity.\(^8\) Some have proposed that internet-based systems combined with TG diagnoses will form a new frame-work to treat both chronic and acute stage patients.\(^11\)

Studies have evaluated the role of TG assessment. For example, a study assessing the feasibility of TG applications found that patients preferred the remote assessment due to the reduced travel, reduced cost and time savings.\(^12\) However, image quality was poorer with TG compared to a university-based clinical examination center.\(^12\) Another study evaluated the use of stereo digital images at primary care centers for review by specialists for glaucoma assessment and found general agreement in the vertical cup-to-disk ratio (VCDR) relative to conventional color stereo-pair slides.\(^13\) The study also found that some images could not be assessed and recommended that a larger study population be analyzed to determine the general overall effectiveness.\(^11\) While the effectiveness, practicality and usage of teleophthalmology techniques are generally accepted, the ability to diagnose glaucomatous ocular disease relative to the clinical slit lamp examination remains unknown.

The current study compares a web-based teleophthalmology technique (TG) to the clinical assessment by an ophthalmologist, for glaucoma screening among diabetic patients in a rural African district.

**MATERIALS AND METHODS**

**Ethics approval**

Ethics approval for this study was granted by the Aga Khan University Research Ethics Committee as part of the Faculty of Health Sciences Medical College in Nairobi, Kenya.

**Patient selection**

The study was carried out in the Muranga District Hospital diabetic and ophthalmology clinics. A precision-based method was used to calculate the appropriate sample size. For an expected sensitivity of 95% and lower limit of 85%, 93 glaucoma cases were needed. A previous study showed that 32% of diabetic patients in Kenya had POAG.\(^14\) Multiplying the two values together, 291 patients were recruited to the study. All patients above the age of 30 years who attended the Muranga Hospital Diabetic Clinic between August 2011 and October 2011 and were capable of giving consent were included in the study. Anyone under the age of 30 years, patients with ocular anatomy (natural or traumatic) inhibiting adequate fundus photography and those with physical deformities that inhibit proper positioning for fundus photography and visual field examination were excluded [Table 1]. Patients were also excluded as needed at the discretion of nurses in cases of potential for aggressive behavior or violence. Blurry fundus photos that were not conducive to TG assessment were excluded.

| Table 1: Inclusion and exclusion criteria |
|------------------------------------------|
| **Type of Criteria** | **Specific Factor** |
|----------------------|---------------------|
| **Inclusion criteria** | >30 years of age |
|                      | Diabetic patient attending Muranga District Hospital Diabetes Clinic |
|                      | Capable of giving informed consent |
|                      | <30 years of age |
|                      | Ocular disfigurement or opacity inhibiting fundus photography |
|                      | Physical deformity inhibiting appropriate positioning for fundus photography and visual field examination |
|                      | Nurse discretion (e.g., violent or agitated patient) |

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Patient prescreening

After obtaining informed consent, patients were escorted to an eye clinic where both a general medical and ocular history was performed by a trained Ophthalmic Assistant (OA) using a predetermined form [Appendix]. The OAs were trained on history taking prior to the study at the Aga Khan University Hospital, Nairobi. Initial ocular assessment conducted by the OA included visual acuity, external ocular exam with a pen torch, IOPs with Tonopen (Reichert Technologies, Depew, NY, USA), Frequency Doubling Technology (FDT) visual field screening perimetry (screening C-20 program), and fundus photography [Appendix]. A photograph of the visual field test printout was uploaded to the computer. Stereo images of fundus were acquired after dilating the pupils with 1% tropicamide. All fundus photography was taken by a Topcon 777 (Topcon Corp., Tokyo, Japan) three field fundus camera at 45°. Each 172 MB (24 bits/pixel) file was 16:1 lossy compressed to a 1.1 MB (1.5 bits/pixel) JPEG image. The OA uploaded the history form, the examination form, the color photographs and the visual fields onto a secure patient data website operated by Secure Diagnostic Imaging (SDI) based in Canada at the University of Alberta (www.teleophthalmology.com). The software, to date, has already been validated for diabetic retinopathy and is utilized for TG at the University of Alberta, Canada. An internet modem from Safaricom Limited was used to access the website. Patients were subsequently subjected to both slit lamp and teleophthalmology examination and results were compared.

Protocol #1: Slit lamp examination

Following pre-screening, each patient was seen by a comprehensive ophthalmologist based in the district. The ophthalmologist reviewed the history form, the examination form and the FDT printout and subsequently completed a dilated fundus exam to diagnose and grade glaucoma, diabetic retinopathy and age-related macular degeneration using the pre-determined form [Appendix]. Lens opacity was recorded based on the Lens Opacities Classification System III classification. During the slit lamp examination, a 90D lens was used to examine the optic nerve in order to record the VCDR and any other features of focal glaucomatous disc damage (notching, rim hemorrhage, peri-papillary atrophy).

Protocol #2: Remote teleophthalmology examination

After uploading the data onto the SDI website, a glaucoma specialist based in Nairobi, reviewed the history form, the examination form, the color photographs, and the visual fields. The specialist viewed the fundus pictures in 3D and manually outlined the rim edge and the cup edge. The software then automatically calculated the VCDR. The specialist also indicated any observed focal rim changes, including rim notching, hemorrhage, and peri-papillary atrophy.

The case definition for glaucoma utilized a combination of the models proposed by Foster et al. and Jonasson et al. for cross-sectional epidemiological research in which the term glaucoma is reserved for people with established, visually significant optic nerve damage. As such, a positive glaucoma diagnosis in the TG analysis was based on a synthesis of history, nerve examination, IOP measurement, and FDT result [Table 2]. The models envisaged that cases of glaucoma would be classified according to three levels of evidence. For a summary of the criteria used to diagnose glaucoma, please refer to Table 2.

Blinding protocol

To ensure a fair comparison, the district comprehensive ophthalmologist doing the in-person fundus exam and glaucoma specialist doing the remote grading were blinded from each other’s findings. Data obtained from the clinical examination, and the SDI program software was entered into Microsoft Excel and SPSS 11.0 (IBM Corp, New York, NY, USA) for analysis and comparison.

Table 2: Levels of glaucoma case definition

| Type of Diagnosis | Optic Feature |
|-------------------|---------------|
| Category 1 diagnosis (structural and functional evidence) 2/3 of the criteria shown with GVFD* | VCDR≥0.7* |
| Category 2 diagnosis (structural evidence only with unproved field loss) 2/3 of the criteria shown | VCDR≥0.8* |
| Category 3 diagnosis (optic disc not clearly seen, field testing unreliable). One of the criteria is shown | Visual acuity<3/60 and IOP>21 mmHg or |
| Glaucosa suspect (one of the criteria shown) | Visual acuity<3/60 and evidence of glaucoma surgery or medical records confirming glaucoma morbidity IOP>23 mmHg* |

*VCDR refers to Vertical Cup-to-disk ratio, GVFD refers to Glaucoma visual field defect and IOP refers Intraocular pressure.
photographs were excluded from the \( \kappa \) analysis. \( \kappa \) values above 0.81 illustrate almost perfect strength of agreement, beyond chance, between 0.61-0.80 illustrates substantial agreement, between 0.41-0.60 illustrates moderate agreement, between 0.21-0.40 illustrates fair agreement and between 0-0.20 illustrates slight agreement.\(^{39}\)

**RESULTS**

**Study population analysis**

The study included 314 patients with a mean age 62 ± 11.6 years. Sixty percent of patients reported a history of hypertension 5% had heart diseases and 5% had asthma, 4% reported consumption of alcohol, and 1% had a history of smoking [Figure 1]. Six percent of the included patients had a history of prior eye surgery and 5% reported a family history of blindness [Table 3]. Four percent of patients reported previously diagnosed glaucoma, and 5% were already using the glaucoma medications. Three hundred and fourteen patients were clinically examined, and 308 patients underwent TG screening. Three hundred and six patients underwent both the clinical examination and TG assessment [Figure 2]. Out of 309 TG optic nerve photos, 74 (24%) were deemed ungradeable. Of the upgradeable cases, 39 were ungradeable due to media opacities: 22 cataracts, 10 corneal opacities, and 7 post-cataract posterior capsular opacities [Table 4]. The other 35 cases were ungradeable due to poor pupil dilation, unsatisfactory photography, and uncooperative patients.

**Comparison of the VCDR grading of the optic nerve head**

The VCDR \( \kappa \) score of agreement (VCDR within ± 0.1) between the TG analysis and the clinical slit lamp examination was 0.55.

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**Table 3: Patient population overview**

| General characteristics | Specific item | Value (percentage of total) (%) |
|-------------------------|--------------|--------------------------------|
| Age (years)             | Mean±SD      | 62±11.6                         |
|                         | SD           | 11.6                           |
|                         | Median       | 63                             |
|                         | Range        | 33-91                          |
| Gender                  | Male         | 124 (40)                       |
|                         | Female       | 187 (60)                       |
| Missing information     |              | 3                              |
| Duration of previous    | Median       | 5                              |
| diabetes mellitus (years)| Range       | 0-44                           |
| Presence of co-         | Hypertension | 188 (60)                       |
| morbidities and risk    | Heart disease| 11 (4)                         |
| factors                 | Asthma       | 15 (5)                         |
| Other systemic          | Alcohol      | 8 (3)                          |
| diseases and            | Cigarette    | 2 (1)                          |
| complications           | smoking      |                                |
|                        | Prior eye    | 18 (6)                         |
| Past ocular history     | surgery      |                                |
|                        | Known        | 11 (4)                         |
|                        | glaucoma     | 17 (5)                         |
|                        | Using        |                                |
|                        | medication   |                                |
|                        | Family       | 15 (5)                         |
|                        | history of   |                                |
|                        | blindness    |                                |
|                        | Mean intraocular pressure | 22±8.5 mmHg |
| Total patient size      | Total        | 314 (100)                      |

**Table 4: Reasons for fundus photograph ungradability \( n = 37 \)**

| Reason                        | \( n \) |
|-------------------------------|---------|
| Cataract                      | 22      |
| Corneal opacity               | 10      |
| Intraocular lens posterior capsular opacity | 7 |
| Others*                       | 35      |

*Including but not limited to dilation difficulty, poor quality photograph, uncooperative patient

**Table 5: Comparison of the agreement in diagnosis of clinical features between teleglaucoma and clinical slit lamp examination in the analysis of both patient eyes**

| Clinical feature               | \( N \) | Kappa (\( \kappa \)) | 95% CI (\( \kappa \)) |
|--------------------------------|---------|-----------------------|------------------------|
| Vertical cup to disc ratio     | 249     | 0.55                  | 0.50-0.61              |
| Notching                       | 239     | 0.31                  | 0.20-0.42              |
| Peripapillary atrophy          | 241     | 0.24                  | 0.11-0.37              |
| Disc hemorrhage                | 235     | 0.25                  | −0.18-0.67             |

*Mean vertical cup to disc ratio in clinical slit lamp examination was 0.6 with standard deviation 0.2. *Mean vertical cup to disc ratio in teleglaucoma assessment was 0.5 with standard deviation 0.1. CI: Confidence interval
Comparison of the detection of focal glaucoma damage

Three types of focal glaucoma damage analysis were conducted: notching, peripapillary atrophy and disc hemorrhage. Agreement between the TG analysis and the clinical slit lamp examination for notching, peripapillary atrophy, and disc hemorrhage was 0.31, 0.24, and 0.25 respectively, indicating fair agreement for these features [Table 5].

Determination of the diagnostic precision for the FDT

In comparing the diagnostic precision of FDT to detect glaucoma in patients with glaucomatous disc damage, as shown with a VCDR > 0.7, the K score of agreement between the TG analysis and the clinical slit lamp examination was 0.84 indicating substantial agreement [Table 6].

Comparison of the ability to diagnose glaucoma

In comparing the ability to diagnose glaucoma, where diagnosis was based on a synthesis of history, nerve examination, IOP measurement, and FDT results, the K score of agreement between the TG analysis and the clinical slit lamp examination was 0.55 with a 95% confidence interval between 0.48 and 0.62 indicating moderate agreement [Table 6].

In the TG arm, the VCDR was electronically generated by a software application that has not yet been validated. In the clinical slit lamp examination, VCDR results showed moderate agreement while other diagnostic features indicating the identification of notching, peripapillary atrophy, and disc hemorrhage, showed fair agreement. In comparing the use of the FDT to detect glaucoma in the presence of VCDR > 0.7, results showed substantial agreement.

Table 6: Comparison of the agreement in diagnosis between teleglaucoma and clinical slit lamp examination in the analysis of both patient eyes

| Assessment                          | N   | Kappa (k) | 95% CI (k) |
|-------------------------------------|-----|-----------|------------|
| Frequency doubling technology       | 263 | 0.84      | 0.79-0.90  |
| Overall glaucoma diagnosis          | 292 | 0.55      | 0.48-0.62  |

CI: Confidence interval

Table 7: Teleglaucoma ability to diagnose glaucoma relative to the clinical slit lamp examination

| Characteristic                      | Value     | 95% CI     |
|-------------------------------------|-----------|------------|
| Sensitivity                         | 41.3      | 30.9-52.6  |
| Specificity                         | 95.8      | 92.1-97.8  |
| Positive predictive value           | 77.5      | 62.5-87.7  |
| Negative predictive value           | 82.2      | 76.9-86.5  |
| Likelihood ratio of positive test   | 9.7       | 4.9-19.5   |
| Likelihood ratio of negative test   | 0.6       | 0.5-0.7    |
| Prevalence of glaucoma by clinical slit lamp (%) | 26 | 20.9-31.1 |
| Prevalence of glaucoma by teleglaucoma (%) | 14 | 9.9-17.9 |

CI: Confidence interval

DISCUSSION

When comparing the ability to diagnose glaucoma between the clinical slit lamp examination and TG assessment, results from this study showed moderate agreement. A positive TG diagnosis of glaucoma carried a 77.5% positive predictive value, and a negative TG diagnosis carried an 82.2% negative predictive value both the relative to clinical examination. In comparing TG analysis with the clinical slit lamp examination, VCDR results showed moderate agreement while other diagnostic features including the identification of notching, peripapillary atrophy, and disc hemorrhage, showed fair agreement. In comparing the use of the FDT to detect glaucoma in the presence of VCDR > 0.7, results showed substantial agreement.

Limitations and implications for future study

Out of 309 photos taken, 74 (24%) were deemed unreadable inhibiting assessment and follow-up. This value illustrates that while a TG approach may increase patient access to glaucoma care, some screening examinations may prove ineffective due to challenges with patient cooperation, media opacities, and technology. Poor quality information including blurry photography can severely limit the effectiveness of TG assessment.

In cases when an appropriate clarity of photography was achieved, there still exists some concern surrounding false negatives indicating that a patient with glaucoma normally diagnosed in the clinical slit lamp examination could be missed in TG assessment. The discrepancy in agreement between the TG analysis and the slit lamp examination may also be the result of differences in physician training and variations in the grading approach. The ophthalmologist seeing the patient in person was a general ophthalmologist whereas, the ophthalmologist grading virtual data was a glaucoma specialist.

In the TG arm, the VCDR was electronically generated by a software application that has not yet been validated. While the SDI software permits a semi-automated calculation of the VCDR, the grader still outlines the disc and cup edge; as such, the calculation is likely different from the manual estimation of the VCDR of the uploaded images with stereo viewer by a glaucoma specialist. Qualitative reports from glaucoma specialists suggest that the lower VCDR presentations could be overrated, and the higher VCDR presentations could be underrated by automatic
software based analysis. Future study should seek to validate this semi-automated SDI-based VCDR tool relative to assessment of the nerve by a glaucoma specialist without using the tool.

While this study shows moderate agreement between the clinical examination and TG assessment, further research is still needed. We suggest that future studies should not only involve a larger patient population in the analysis, but that the same ophthalmologist completing the slit lamp examination be one grading images virtually. By using the same ophthalmologist, with some time lapse to reduce recall bias, inter-observer variation and the effect of variable training can be eliminated.

Finally, our population was enrolled from a diabetic clinic and therefore, does not provide true prevalence of glaucoma in the population. Future investigation comparing TG assessment and the clinical slit lamp examination could be conducted in population-based studies in order to determine the power of TG at detecting cases.

Relation to the literature
As discussed above, while the effectiveness, practicality, and usage of teleophthalmology techniques are generally accepted, there exists a dearth of knowledge surrounding its ability to diagnose glaucomatous ocular disease in particular. We were unable to find other studies to compare our findings. Our study has helped shed light upon the ability for teleophthalmology applications specifically within the field of glaucoma and in the assessment of the optic nerve damage.

CONCLUSIONS
In conclusion, virtual grading of patient history combined with structure and function information to diagnose glaucoma produces moderate agreement with in the person clinical examination. Independent assessment of the VCDR showed moderate agreement while assessment of notching, peripapillary atrophy, and disc hemorrhage produced fair agreement. Furthermore, the use of FDT C-20 screening protocol to detect glaucoma in the presence of glaucomatous disc damage with a ratio of greater than 0.7 proved to have substantial agreement and can be used in screening and diagnosis. We also conclude that poor quality information including blurry fundus photography can severely limit the ability of TG assessment to diagnose optic nerve damage and glaucoma. Although further validation is needed, the TG approach provides a novel and promising method to diagnose glaucoma, a major cause of ocular morbidity throughout the world.

ACKNOWLEDGMENTS
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Appendix

| History Forms |
|---------------|
| Date: ____________ |
| Name: ______________ | Project No: ______________ | DOB: ______________ | M/F: ______________ |

| History | RE | LE |
|---------|----|----|
| Known glaucoma | Y/N | Y/N |
| Current ocular meds | | |
| Eye surgery | Trab/Cataract–Intraocular Lens Aphakia Others | Trab/Cataract–Intraocular Lens/Aphakia Others |
| Family history of glaucoma | | |

| Systemic history |
|------------------|
| Systemic medication | |
| Duration of diabetes | |
| Hypertension | Y/N |
| Heart disease | Y/N |
| Asthma | Y/N |
| Alcohol consumption | Y/N |
| Cigarette smoking | Y/N |
| Any other systemic disease | |
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