



**The prevalence and determinants of diabetic
retinopathy in Botswana: findings from a screening
programme.**

DR NURU SAID OMARI

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Supervisors: Professor Colin Cook

Dr Oathokwa Nkomazana

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RESEARCH PROTOCOL

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1.1 Protocol Executive Summary

1.1.1 Background

The International Diabetes Federation (IDF) estimates that the number of adults with diabetes in Africa will escalate from 12.1 million to 23.9 million by the year 2030, a 98% increase¹. Diabetic retinopathy (DR) has become a significant cause of blindness in developing countries because of longevity and decline in the other preventable causes of blindness². DR diagnosed early, followed closely, and treated timeously with retinal laser therapy, prevents blinding proliferative retinopathy³. The effectiveness of this treatment suggests that there is the potential for a national screening programme to bring about a major reduction in blindness⁴ from DR in Botswana.

1.1.2 Objectives

This study of 223 participants will attempt to determine:

1. The prevalence of DR among diabetics that present for screening.
2. The accessibility and acceptance of this screening programme.
3. Risk factors that are potential predictors of DR.

1.1.3 Methods

A cross-sectional observational study design will be used with participant recruitment from diabetic patients attending the Gaborone Block 6 screening centre over a 5-week period. The participants will be interviewed using a questionnaire to determine; whether they have retinopathy, to collect baseline socio-demographic data as well as their access and acceptance of the screening service. Descriptive data will be reported for the predictor variables collected and a multivariate analysis will also be done to determine the risk factors associated with retinopathy.

1.2 Introduction

1.2.1 Diabetes mellitus- Significant public health problem

The World Health Organisation (WHO) estimates that there are more than 170 million people with diabetes mellitus (DM) worldwide and this figure is expected to rise to 366 million in 2030. The most rapid growth is expected in low and middle income countries amongst working age populations⁵.

The International Diabetes Federation (IDF) has estimated that the number of adults with DM in Africa will increase from 12.1 million to 23.9 million by the year 2030, a 98% increase. This is believed to be driven by the increase in urbanisation, sedentary lifestyles, obesity, population overgrowth and aging- as well as successes in combating communicable diseases in the region¹. Sub-Saharan Africa, like the rest of the world, is experiencing an increasing prevalence of diabetes alongside other non-communicable diseases⁶. In addition, the region is still grappling with high rates of persistent communicable diseases such as HIV, TB and malaria⁷. DM must therefore compete for political attention and the limited financial resources.

1.2.2 Diabetic retinopathy- A complication of Diabetes Mellitus

Diabetes causes visual impairment through cataract and diabetic retinopathy (DR); a progressive disease of the retinal microvasculature. Retinopathy is thought to evolve through several stages, with background retinopathy progressing to maculopathy or proliferative retinopathy or a combination of the two⁸. Both maculopathy and proliferative retinopathy can independently lead to blindness. The challenge with DR is that it remains asymptomatic until it reaches advanced stages causing blindness in diabetic adults' aged 20–74 years⁹. Without treatment, 50% of patients with retinopathy will become blind within 5 years¹⁰. The Diabcare Africa study carried out in 6 specialised diabetes centres found background retinopathy to be the leading eye complication [18%] followed by cataract [4%], amongst diabetic patients attending these centres¹¹.

1.2.2.1 Global estimates of diabetic retinopathy

The importance of DR as a cause of blindness has increased because of the rise in DM prevalence, longevity and the decline in other preventable causes of blindness in developing countries². DR is the fifth leading cause of blindness, globally affecting an estimated 1.8 billion people and is responsible for 4.8% of the blindness worldwide¹².

In recent years, due to better access to high quality cataract surgical services, DR is becoming a more significant cause of blindness¹¹.

1.2.2.2 African estimates of diabetic retinopathy

In Africa, the prevalence of DR ranges from 17.9% in West African diabetic population¹³ to 40.3% in rural regions of South Africa¹⁴.

The latter study found that the complication rate among rural South Africans was high and that more than 1 in 10 diabetics had severe retinopathy requiring laser. In 2012, a systematic review of the studies done in 21 African countries¹⁵ reported the prevalence of any retinopathy in patients with diabetes to be between 30.2-31.6%. The review also found proliferative DR to be 0.9-1.3% and maculopathy 1.2-4.5%.

1.2.3 Determinants and treatment of diabetic retinopathy

The main risk factors for development of diabetic retinopathy are age, duration of diabetes and level of glycaemic control⁴. Photocoagulation is a very effective treatment in the prevention of blindness from sight threatening DR. Data from several randomised controlled trials (RCTs) performed in Europe and North America have shown that photocoagulation reduced the risk of blindness by up to 61% in the treated eye¹⁶. The effectiveness of this treatment suggests that there is the potential for a national screening programme to bring about a major reduction in blindness from retinopathy⁴.

1.2.4 Situational analysis in Botswana

Botswana, with a population is just over 2 million, has developed from one of the least developed countries at independence in 1966 to an upper-middle income country mainly due to its prudent use and management of mineral resources and a stable democratic government system¹⁷. Despite this, Botswana continues to face multiple challenges such as high HIV prevalence rates with an estimated sero-prevalence of 37% amongst adults; high mortality rates among both women and children; persistent poverty and high unemployment¹⁸.

There has not been a study to determine the number of diabetics living in the country but using WHO global estimates for a middle income country, the prevalence is conservatively estimated to be 4% of the population,¹⁹ which translates to 80 000/2 000 000. Using prevalence of DR rate of 20% (8 000 per million population) and among these, it is estimated 5% will be blind (400 per million population).

The only population based study to date, looking at visual impairment nationally found DR to be the second leading cause of blindness (20%) after cataract in adult's aged 50 years and above²⁰. Most of the prevalence data of DR from Botswana is limited to a few, mostly hospital/facility based studies. A survey in 2006 of diabetics attending a health facility in Botswana estimated the prevalence of retinopathy to be only 9.2% and was the third most common eye condition after refractive error and cataract²¹.

Another study completed in 2011, found the prevalence of DR to be 17.7% among the diabetics on the national screening register in Botswana²².

1.2.4.1 Diabetic retinopathy screening service (DRSS) in Botswana

Retinopathy diagnosed early, followed closely and treated timeously with retinal laser therapy prevents blinding proliferative retinopathy and most importantly blindness³. Therefore, both the IDF and WHO vision 2020 guidelines recommend early detection of DR by means of DR screening. The DRS Service in Botswana was developed by prevention of blindness program (PoB) in the ministry of health in October 2009 with the help of a UK based charity called Addenbrook's Abroad²³.

The screening was first done at Princes Marina hospital, a Referral facility in Gaborone until end of 2011 when it moved to Block 6 clinic. The DRSS went national in 2012 and included 3 additional screening sites, Donga Clinic in Francistown, Sekgoma Memorial Hospital in Serowe and Letsholathebe Hospital in Maun. Block 6 Clinic is still the designated “diabetic centre of excellence” and offers a comprehensive array of services for the overall management of diabetic patients. The DR screening is done by 2 trained ophthalmic nurses using a non-mydratic fundus camera. The nurses have also been trained to grade the pictures. However, attendance has been consistently low at the clinic and the “did not attend” (DNA) rate is estimated to be around 30% .²³

1.3 Rationale

Despite the low attendance rates for DR screening, the Botswana DRS programme has been expanded from one to four centres. This research therefore will provide useful information about the acceptability of this service to patients in Botswana. Additionally, the study may shed light into potential strategies to strengthen the programme. Data on DR from African settings is quite limited hence the results of this study will add to the available information on the disease in an African country.

1.4 Study Objectives

The primary objective of the study is to determine the prevalence of DR, its determinants and the accessibility of the screening services in a sample that is presumed to be representative of the diabetic community attending screening at Block 6 clinic.

The following objectives are outlined for the study:

1. To determine the prevalence of any DR in the patients screened at the centre.
2. To determine the prevalence of referable DR amongst those that present to the screening service.
3. To assess how well the patients presenting for screening manage their diabetes.
4. To determine the level of awareness of the availability of screening services.
5. To assess how acceptable the screening services are to the patients.
6. To explore the association between diabetic retinopathy on fundus camera findings and other predictor variables.

1.5 Methodology

1.5.1 Study design and setting

The study is a cross-sectional study to be conducted at Gaborone Block 6 diabetic retinopathy screening clinic. The study will be for 5-weeks and will include every patient that arrives for DR screening services during that time and has consented to be included in the study.

1.5.2 Population and recruitment

The study population will be any diabetic above the age of 18years presenting to the eye clinic. Convenience sampling will be used where consecutive patients will be asked to participate in the study. Participation will be voluntary and no form of incentive will be provided for agreeing to enrol into the study. Eligible participants will be recruited from the clinic waiting area where explanation of the study and consent will be sought. The questionnaire will then be administered by the researcher(s) to each participant in one of the rooms available for use in the eye clinic.

1.5.3 Inclusion Criteria

Any patient arriving at block 6 clinic for screening for diabetic retinopathy with all the following can be enrolled into study:

- Age of 18 years or older
- Physician diagnosed Type 1 or type 2 DM.
- Ability to give written informed consent for participation in the study.
- Referred to Block 6 from any another health facility, whether private or public.
- First time/repeat patients

1.5.4 Exclusion Criteria

- Pregnant females with gestational diabetes.
- Patients travelling alone who are unable to speak or with speaking difficulties that may hinder understanding of the researcher.

1.5.5 Sample size

The sample size is calculated using the expected prevalence of any retinopathy and maculopathy in the diabetic population to be 17.7%. This is based on a previous local study of the diabetics on the national screening database¹². In addition to the expected proportion we will use a precision of 5% and a power of 80%.

$$n = \frac{p(1-p)z^2}{d^2} = \frac{0.177(1-0.177)1.96^2}{0.05^2} = 223$$

1.5.6 Data collection tools

1.5.6.1 Questionnaire

Since no existing validated tool exists that would meet all the study objectives, a questionnaire based on a review of the literature was developed.

The questionnaire was developed in English but has also been translated into Setswana, which is the National language of Botswana. Most young people in Botswana can understand some form of English but since the majority of the study sample will be elderly, there is need for translating the data collecting tools to avert difficulty in communication. Once the information has been captured in Setswana services of a professional translator will be utilised to back translate to English so as to ensure accurate capturing of the information provided by the participants.

The questionnaire contains 3 sections:

- a. Demographic data
- b. Diabetic management information
- c. Awareness and access to screening service

The designed questionnaire was piloted at the Block 6 diabetic centre of excellence clinic, with 8 participants. These were diabetics attending the clinic for a variety of reasons, not necessarily for DR screening.

The purpose of the pilot was to determine whether the questions are understandable and interpreted as expected by participants. The tool was re-conceptualised following the pilot study to make sure that it captured what it was expected to.

1.5.7 Reliability and Validity

There is no validated questionnaire linked to our specific research question to ensure validity however, the tool has face and construct validity in that literature was reviewed to determine the variables affecting diabetics that choose to present at screening centres. Authors of similar studies were contacted and requests of the questionnaires they used were made to guide the development of our study questionnaire.

Reliability was ascertained by piloting the survey to 8 patients attending the Diabetic centre of excellence in Gaborone. The questionnaire was translated into Setswana by the ophthalmic nurses who work at the clinic. This helped remove the communication barrier between interviewer and participant hence allowing for repeatability in responses.

1.5.8 Potential study biases

Study participants will be selected as they enter the clinic via convenience sampling hence possibly prone to selection bias. Therefore, those patients that already present to health facilities for treatment will be selected to enter study whilst others out in the community who do not routinely attend health facilities might be missed. There may be study relevant differences between patients who attend and those who don't. Information bias can affect the study because the questionnaire is administered by the researcher, who is a doctor, and the participants might give responses that are socially acceptable rather than the truth. Especially in regards to their management of diabetes, patients may not be forthcoming if their management is not optimal.

Associations between retinopathy and the predictor variables is prone to confounding because this is a prevalence study and causal relationships are a challenging to determine in such a study design.

1.5.9 Measurement

The main outcomes of interest are the number of diabetic participants with DR as a proportion of the study sample. We will analyse different predictor variables to determine their effect on the risk of DR in diabetic patients.

Table 1.1: The list and definition of variables that will be considered in the study.

Name	Scale	Possible Values
DEMOGRAPHICS		
Age	Numerical - continuous	≥ 18 years
Sex	Categorical - binary	male, female
Fundus camera findings	Categorical - nominal	no retinopathy, any retinopathy, referable retinopathy
Household occupants	Numerical - continuous	≥ 1
Marital status	Categorical - nominal	single, married, divorced, widowed
Education level	Categorical - nominal	none, primary, secondary, tertiary
Employment status	Categorical - binary	yes, no
DM MANAGEMENT		
Duration of DM in years	Numerical- continuous	> 0
On treatment/not on treatment	Categorical - binary	yes, no
DM knowledge	Categorical - ordinal	poor, average, good
DM medication	Categorical - nominal	diet & exercise, oral meds, injectable, oral & injectable
DM medication compliance	Categorical - ordinal	never, sometimes, most times, always
DM alternative medicine	Categorical - binary	yes, no
SCREENING SERVICE ACCESS		
Screening service access	Categorical – nominal	< 30 minutes, 30-60 minutes, > 60 minutes
Screening history	Categorical - binary	yes, no
Time of last screening	Categorical - nominal	first, 0-12 months, 12-24 months, > 24 months
Reasons for delayed screening	Categorical - nominal	cost, distance, forgot, busy
Appointment scheduled	Categorical - binary	< 1 month, > 1 month
Understands screening reasons	Categorical - binary	yes, no

1.5.10 Potential benefits of study participation

The benefits of participating in the study are that participant has an opportunity to speak about the non-clinical aspects of their condition and its management. Due to time and inadequate staffing constraints, it is not very often that patients are asked about their barriers to accessing quality health care. Study participants also inherently benefit from screening because a positive screening test would result in early management of the DR to avoid rapid progression to blindness.

1.6 Data management plan and analysis

Data will be collected by study personnel and recorded in participant questionnaires for entry into a Microsoft Excel database for storage. The data will be cleaned using pivot tables in excel and exported to STATA version 14.1 (Stata Corp. College Station Texas) for analysis. Raw data will be stored in a specified locked cupboard in Block 6 Clinic and only named study staff will have access to it. Each participant will be assigned a unique study number. The Microsoft Excel database will only use the study number and not the name of participant.

The correlation between study number and respective name will be kept in the raw data format in a file that will be locked away at the study site. Confidentiality will be maintained at all times in the study and the name, address, telephone number, or any other direct personal identifiers will not identify the participant in the study records, except when required by law. The data collected remains the property of the ministry of health- Diabetic retinopathy screening programme.

Basic descriptive statistics of the study sample will be reported i.e. age, sex, marital status, fundus camera findings, level of education and employment status. For each participant we will also report their overall DM management and their access to DR screening services.

1.6.1 Objective 1

We will report the prevalence of participants with any DR as a proportion of the study sample.

1.6.2 Objective 2

We will report the prevalence of participants with referable DR as a proportion of the study sample.

1.6.3 Objective 3

We will report the number of participants in the different variables under the section of DM management (see Table 1.1) as a proportion of the study sample.

1.6.4 Objective 4

We will report the number of participants in the different variables under the section of screening services access (see Table 1.1) as a proportion of the study sample.

1.6.5 Objective 5

We will report the number of participants in the different variables under the section of screening services access (see Table 1.1) as a proportion of the study sample.

1.6.6 Objective 6

We will perform a multivariate analysis with DR as the outcome of interest on the various risk factors collected from the participants to determine their association with the DR outcome.

1.7 Ethical considerations

The primary ethical issues for the study are:

1.7.1 Consent

All participants above the age of 18 years will be required to give consent prior to entering the study. Consent will be taken in the participants' language of choice and the consent forms will be available in English and Setswana. Consent will cover all aspects of the study, including data collection and reporting.

The consenting process will consist of a detailed verbal description of the study as well as a written consent form and information sheet. Consent forms will be in triplicate, with one copy for the participant, one for the study personnel, and one for the study folder.

1.7.2 Respect for persons

Participation in the study is voluntary and participants may withdraw their participation from the study at any time.

1.7.3 Privacy

The interviews will take place in a side room next to the eye clinic which has been kindly offered by the ophthalmic nurses for research purposes. In the room there will be a participant (with a family member if they request), 1 researcher who will administer the questionnaire and the translator if required.

1.7.4 Confidentiality

The questionnaire will have a name but only to triangulate the data with the retinal findings in the nurses log book, if need be. The health care worker who will assist with the translation into Setswana will also subscribe to the ethical conduct that governs their everyday practice at the clinic.

The information gathered will only be seen by the study staff and nominated personnel involved with the analysis. When all the identifying data has been removed from the data, then the findings of the study may be shared with other stakeholders, if requested.

1.7.5 Beneficence

There is always the minimal risk of loss of confidentiality as with any study but no significant potential harm to the participants is foreseen in this study. As this is an observational study where participants will be asked about their knowledge of DR screening and diabetes care, participants may actually feel relieved that they have an opportunity to share their experience of their disease. After the questionnaire is administered, the participant may ask a few questions regarding the study, DRSS or DR. This allows for knowledge sharing with the participant as the researchers are well acquainted with the structure of the eye services in the public health sector.

1.8 No fault insurance

The participants in this study are covered by the no-fault insurance offered by the University of Cape Town. The participants' parents or guardians will be informed of this during the consenting process and it is specified in writing on the information sheets. The University of Cape Town (UCT) undertakes that in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity, that is caused by your participation in the study, it will provide immediate medical care.

UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly-speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault.

An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications. UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. However, it has to be noted that this study poses very little risk in terms of the health and well-being of the participants since it is not an intervention trial.

1.9 Funding

The study does not have much expense hence the funding is will be covered by the Principal Investigator through her own expenses.

1.10 Stakeholders and Dissemination strategy

The University of Cape Town is the primary stakeholder as the research protocol has to successfully meet the ethical standards when dealing with human research. The school of public health and particularly the community eye health department will be very interested in the findings of this study as I am the first candidate to enrol into the Master of Public Health - Community Eye Health stream.

The Botswana Ministry of Health (MOH) also requires the research protocol to be submitted to their ethics committee for approval. Seeing as the study will be based in one of the health facilities, the findings will be relevant to them and hence making them a significant stakeholder. Findings will be disseminated to the various stakeholders in the form of a preliminary report, and presentations at appropriate meetings and conferences if requested. An article will be submitted to a public health/eye health peer-reviewed journal. The abstract will also be submitted to the community eye health journal (CEH) read by ophthalmic health care workers in resource constrained regions of the world.

1.11 Logistics

Provisional enquiries have indicated that there are on average 15-20 adults per day are screened at the Block 6 Clinic. We aim to recruit all patients that present for screening (averaging 90 participants per week) and depending on the response rate (assumed to be >80%) the data collection for the study is likely to be completed within 1 month (November 2014-December 2014). This time frame takes into consideration factors like slow recruitment rates amongst other challenges that could be encountered as the study progresses.

An outline of the proposed study time is given below:

January 2015-February 2015 Data collection and Data capturing

December 2015 Data cleaning and Baseline data exploration

January 2016-March 2016 Final analysis, preparation of manuscript

March 2017 Submission

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1.13 Appendices

1.13.1 Letter of Consent



SCHOOL OF PUBLIC HEALTH AND FAMILY MEDICINE

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

University of Cape Town

Observatory 7925

South Africa

27 October 2014

STUDY INFORMATION SHEET

The prevalence and determinants of diabetic retinopathy in Botswana: findings from a screening programme.

I am a graduate student enrolled with the University of Cape Town and am conducting a research study as part of the requirements of the Master's degree in Public Health.

My study will be looking at Diabetic Retinopathy (DR) which is a disease that may cause visual impairment or even blindness in Diabetics. In DR, the high levels of sugar in the blood can cause damage to the blood vessels in the back of the eye (retina) which then affects the vision. The risks for developing DR are increased number of years lived with the disease as well as poor control of blood sugar.

DR is a painless disease and most times people are not aware that there is any damage until their vision begins to deteriorate. Therefore, all diabetics are encouraged to attend for annual screening for DR which involves checking the vessels of the retina for early changes with a camera.

If no changes are seen, you will be asked to continue attending for annual DR screening and continue to take good control of your blood sugar. If any changes are seen, you will be sent to a specialist eye doctor who may perform laser treatment to the back of the eye.

Purpose of the study

- To determine the prevalence of Diabetic retinopathy amongst those attending for screening at block 6 Clinic.
- How well do those that present for screening manage their Diabetes
- Lastly, the acceptance as well as the access of the screening programme by patients/diabetics in Botswana will also be assessed.

You are invited to take part in our study as we believe that your input would be valuable for our study and improve our knowledge and understanding about the issues affecting Diabetics with regards to screening their eyes for Diabetic retinopathy. This information can be used to improve the programme and hopefully contribute towards reducing blindness from Diabetic Retinopathy in Botswana.

Procedures

If you volunteer to participate in this study, we would ask you to be available for a brief (10 minute) interview with the researcher(s) at Block 6 Clinic.

In order for the retina to be seen clearly, some eye drops will be instilled into your eye before the eye examination. These drops will help dilate the pupil of your eye, which is the black hole in the front of the eye.

Potential risks and discomforts

The eye drops used for dilating the eye may cause sensitivity of light to the eye. This is temporary and the effects should wear off after an hour or two. You may wear sunglasses if you still feel some sensitivity to the light. If you continue to experience the sensitivity please inform one of the eye nurses who will assist you accordingly.

Potential benefits to subject

There are no direct benefits to you, financial or otherwise, for participating in this study.

Confidentiality/Privacy

Your involvement in this study is for research purposes only. All the data collected in this study will be treated as strictly confidential. No names will be used in the publications

Confidentiality will be ensured by making the collected data available only to the main researchers, research assistants and participants themselves.

Rights of study participant

Your participation is entirely voluntary (of your own choice) and refusal to participate will not be held against you. There will be no penalty in the event that you decide to withdraw from the study or refuse to answer any question that you feel uncomfortable answering.

You are not waiving any legal claims or rights because of your participation in this research study. Please feel free to ask any questions regarding your rights as a research participant and any concerns you may have. If you understand and are satisfied with the information above, and wish to take part in the study, please fill in your name and signature and return the Consent Form below.

If you have any further inquiries regarding the study please feel free to contact any of the researchers listed below.

Dr Nuru Omari – nuru.hussein@gmail.com or mobile number (+267) 73792033

Prof Cook - colin.cook@uct.ac.za

Dr Nkomazana- nkomazanao@mopipi.ub.bw

You may also contact the University of Cape-Town (UCT) Human Research Ethics Committee (HREC) on 021 406 6338 in case participants have any questions regarding their rights and welfare as research subjects on the study.

CONSENT FORM FOR PARTICIPATION IN THE STUDY

The information above was described to me by _____ in _____ and I am fluent in this language.

I hereby voluntarily agree to participate in the research study. The purpose and procedures of the study have been explained to me. I understand that my participation is voluntary and that I may refuse to answer any particular items or withdraw from the study at any time without any negative consequences. I also understand that my responses will be kept confidential.

Name of participant: _____ Date: _____

Signature: _____

1.13.2 Participant questionnaire

PARTICIPANT QUESTIONNAIRE

PARTICIPANT DETAILS

Q1	Name of participant	
Q2	Participant ID	0000/XX
Q3	Enrolment date	DD/MM/YYYY
Q4	Home (Living) Address	_____ _____
Q5	Contact Number	
Q6	Age at enrolment	00 years
Q7	Sex	1=Male 2=Female

FUNDUS CAMERA

Q8	Fundus camera findings?	1 = no retinopathy	2 = any retinopathy	3 = referable retinopathy
-----------	-------------------------	--------------------	---------------------	---------------------------

DEMOGRAPHIC DATA

HOUSEHOLD CHARACTERISTICS

Q9	How many people live with you at home?	1 = 1-5 people	2 = 6-10 people	3 = >10 people
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MARITAL STATUS

Q10	What is your current marital status?	1 = single, never married	2 = married/ domestic partnership	3 = divorced	4 = widowed
------------	--------------------------------------	---------------------------	-----------------------------------	--------------	-------------

EDUCATION LEVEL

Q11	Highest education level attained?	1 = never attended school	2 = completed primary school	3 = completed secondary school	4 = tertiary level
------------	-----------------------------------	---------------------------	------------------------------	--------------------------------	--------------------

EMPLOYMENT STATUS

Q12.1	Are you currently employed?	0 = no	1 = yes
Q12.2	If Yes, what is your occupation?		

DIABETES MELLITUS MANAGEMENT

DM HISTORY

Q13	How many years have you been living with DM?	
------------	--	--

DM MANAGEMENT

Q14	Do you regularly get followed up by your doctor for DM management?	0 = no	1 = yes
------------	--	--------	---------

CARETAKER

Q15	Who helps you take care of your health?	1 = I take care of myself	2 = spouse	3 = child	4 = non-relative
------------	---	---------------------------	------------	-----------	------------------

DIABETES KNOWLEDGE

Q16	How do you rate your understanding of Diabetes?	1 = poor	2 = average	3 = good
------------	---	----------	-------------	----------

DM MEDICATION

Q17.1	What DM treatment are you currently taking?	1 = diet & exercise control	2 = oral medication only	3 = insulin only	4 = oral & injectable
Q17.2	If none of the above, please explain why?				

MEDICATION COMPLIANCE

Q18	Do you regularly use your treatment as directed by your health care provider?	1 = never	2 = sometimes	3 = most times	4 = always
------------	---	-----------	---------------	----------------	------------

ALTERNATIVE MEDICINE

Q19.1	Are you taking any traditional medicine for your DM?	0 = no	1 = yes
Q19.2	If so, what are you taking?		

ACCESSIBILITY OF SCREENING SERVICES

ACCESS

Q20	How far did you have to travel to come here today?	1 = <30 minutes	2 = 30-60 minutes	3 = >60 minutes
------------	--	-----------------	-------------------	-----------------

SCREENING HISTORY

Q21	Is this the first time having a picture taken of the back of your eyes?	0 = no	1 = yes
------------	---	--------	---------

Q22	When was the last time you had a picture of the back of your eyes taken?	1 = 1 st time	2 = 0-12 months ago	3 = 13-24 months ago	4 = >24 months ago
------------	--	--------------------------	---------------------	----------------------	--------------------

Q23	If >12 months ago, what was the reason for the delay?	1 = cost	2 = distance	3 = forgot appointment	4 = busy at the time	5 = Other
------------	---	----------	--------------	------------------------	----------------------	-----------

Q24	This time, how long ago were you told to come here?	1 = <1 month ago	2 = > 1 month ago
------------	---	------------------	-------------------

Q25	If >1 month ago what was the reason for this delay?	1 = cost	2 = distance	3 = forgot appointment	4 = busy at the time	5 = Other
------------	---	----------	--------------	------------------------	----------------------	-----------

Q26	Do you feel you understand the importance of this service to diabetics?	0 = no	1 = yes
------------	---	--------	---------

1.13.3 Ethics approval letter



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: shunetta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 December 2014

HREC REF: 893/2014

Prof C Cook
Ophthalmology
Ward D4
NGSH

Dear Prof Cook

PROJECT TITLE: THE PREVALENCE AND DETERMINANTS OF DIABETIC RETINOPATHY IN BOTSWANA: FINDINGS FROM A SCREENING PROGRAMME (Masters candidate Dr -N Omari)

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 11 December 2014.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Nuru Said Omari will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

HREC 893/2014

1.13.4 MEAJO Journal Submission Guidelines

✓ MANUSCRIPT PREPARATION

The entire manuscript must be double-spaced with 1" (2.5cm) margins. Number pages in upper right corner. Pages should be numbered consecutively, beginning with the title page and continuing to the last typewritten page. Insert line number (use continuous line numbering feature of the MS Word)

First Page/Title Page

The title page must contain (1) title of the article in English with the capitalization of only the first letter of each word, (2) listing the correct order of authors using first and family names, the middle initial is optional followed by the highest level of degree; if authors are from various institutions, indicate by numerical superscripts, and list institutions below the author names, (3) disclosure of monetary grants or sponsoring organizations should be indicate, (4) provide the complete name, mailing address, fax, phone number and email to whom inquiries should be sent if it differs from the first author.

Abstract

Original Articles: Include a summary (not more than 250 words) in a structured format (PURPOSE, METHODS, RESULTS, CONCLUSION). Abstracts have no reference numbers and avoid use of abbreviations.

Brief Communications: Include a summary (not more than 200 words) in a structured format (PURPOSE, METHODS, RESULTS, CONCLUSION). Abstracts have no reference numbers and avoid use of abbreviations.

Review Articles: Include a summary of (not more than 250 words) in unstructured paragraph form. Abstracts have no reference numbers and should avoid abbreviations.

Case Reports: Include a summary (not more than 150 words) in unstructured paragraph form. Abstracts have no reference numbers and avoid use of abbreviations.

Text

Introduction: A brief introductory statement should state the objective and intent for presenting this information. This should not include exhaustive review of the literature but only that portion which is pertinent to the purpose of the study.

Material and Methods: Describe precisely and clearly how and why as if to be replicated. In studies of diagnostic accuracy, the methods should include the inclusion and exclusion criteria of the patients involved in the study as well as disclosing the methods of recruitment. Include a statement on IRB/EC approval, and, indicate whether or not the study adheres to the tenets of Declaration of Helsinki. The journal reserves the right to ask for proof of IRB approval.

Results: Clear presentation of all findings in a logical manner. Use of statistical and mathematical analyses, combined with tables and figures to show results.

Discussion: Comments should be elucidated from the results and limited to significance of the data. Limit the word count to a maximum of 1000 for original articles. Conclude the discussion with a summary of the paper.

Avoid using sub-titles and bullet text in all sections.

Acknowledgement

Acknowledgements, if any, should be included in the First Page/Title Page file and not in the main Article file. It should conform to the Uniform Requirements for Biomedical Journals which states: List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged. Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators", and their function or contribution should be described, for example, "served as scientific advisors" "critically reviewed the study proposal", "collected data" or "provided and cared for study

SECTION B
STRUCTURED LITERATURE REVIEW

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ABBREVIATIONS

DM	Diabetes mellitus
IDDM	Insulin dependent diabetes mellitus
NIDDM	Non-insulin dependent diabetes mellitus
DR	Diabetic retinopathy
DME	Diabetic macular Oedema
STDR	Sight threatening Diabetic Retinopathy
DRS	Diabetic retinopathy screening/ Diabetic retinopathy study
ETDRS	Early treatment diabetic retinopathy study
DRSS	Diabetic retinopathy screening service
NCD	Non communicable diseases
PI	Protease inhibitor
ART	Antiretroviral therapy

2. Literature Review

2.1 Introduction

2.1.1 Definition and classification of Diabetes

The term diabetes mellitus describes “a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both”¹. The long term exposure to hyperglycemia is associated with damage, dysfunction, and failure of various end organs, particularly the eyes, kidneys, nerves, heart, and blood vessels².

Classification of Diabetes Mellitus (DM) is more accurate if based on clinical progression and aetiology hence previously used terms such as insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) have been eliminated from the current terminology³. These terms were a cause of confusion and frequently resulted in patients being classified based on treatment rather than pathogenesis. Following the expert committee meeting on the diagnosis and classification of DM, the terms type 1 and type 2 diabetes mellitus replaced IDDM and NIDDM, respectively⁴.

2.1.2 DM- Significant public health problem

The World Health Organisation (WHO) estimates that there are more than 170 million people with diabetes mellitus (DM) worldwide and this figure is expected to rise to 366 million by the year 2030. The most rapid growth is expected in low and middle income countries amongst working age populations⁵. Currently, more than two thirds of people with diabetes live in low and middle income countries⁶.

The International Diabetes Federation (IDF) has estimated that the number of adults with DM in Africa will increase from 12.1 million to 23.9 million by the year 2030, a 98% increase. This is believed to be driven by increasing urbanisation, sedentary lifestyles, obesity, population overgrowth and aging- as well as successes in combating communicable diseases in the region⁷. Therefore, it is not surprising that there is a variation in prevalence frequently observed between rural and urban populations^{8:9} with the latter showing higher prevalence of diabetes mellitus. A survey in Kenya recorded DM prevalence rates of 2% in rural regions compared to 12% in urban regions¹⁰. Sub-Saharan Africa (SSA), like the rest of the world, is experiencing

an increasing prevalence of diabetes alongside other non-communicable diseases, a so called “double burden” of disease¹¹.

The region is still grappling with high rates of persistent communicable diseases such as HIV, TB and malaria¹², DM must therefore compete for political attention and the limited financial resources. Type 2 diabetes is the predominant form of diabetes in SSA and accounts for more than 90% of the cases, whilst type 1 diabetes mellitus, gestational diabetes and other specific types constitute less than 10%¹³. Risk factors for the development of T2DM include obesity, ageing, and physical inactivity, often arising as a result of socioeconomic dynamics¹⁴. Recent evidence suggests that antiretroviral treatment is associated with an increase in obesity and insulin resistance¹², showing that communicable and non-communicable diseases are not separate entities as once considered. Conversely, the risk for infections such as pneumonia, TB and sepsis are also likely to increase in the Diabetic population¹⁵.

2.1.3 TB and HIV infections associated with Diabetes Mellitus

HIV infected persons are at increased risk of developing type 2 DM because of viral coinfection and adverse effects of treatment¹⁶. Protease inhibitor (PI) therapy for HIV-1 infection is in some cases associated with lipodystrophy syndrome in which type 2 DM and hyperglycaemia is a feature¹⁷. A prevalence of lipodystrophy of upto 83% in one study after only 21 months was concerning since ARV treatment is intended to be lifelong¹⁷. The same study found Diabetes mellitus was diagnosed in 7% of protease inhibitor recipients and impaired glucose tolerance in a further 16%. Recent data shows that another class of ARVs, the nucleoside analogue reverse transcriptase inhibitors (NRTI), also contribute to increased insulin resistance¹⁸.

In recent decades, tuberculosis has increasingly become a problem in low-income countries, particularly those with HIV epidemics¹⁹. Despite the availability of effective therapy, tuberculosis (TB) continues to infect an estimated one-third of the world’s population, causing disease in 8.8 million people per year, and 1.6 million of those afflicted end in fatality²⁰. A number of large studies involving thousands of participants provide convincing data that diabetes mellitus is a moderate-to-strong risk factor for the development of active tuberculosis

21;22;23

A WHO review done in 2008 found that diabetics compared to non-diabetics had a 3-fold risk of developing active TB²⁴. In the setting of the increasing populations at risk of both diseases, the combination of TB and DM represents a worldwide health threat but particularly in developing nation where health systems struggle to meet the health challenges²⁵.

2.1.4 Diabetes and Obesity

WHO estimates that globally there are more than 1 billion overweight adults and at least a third of them are obese²⁶. Until recently, it has been perceived that obesity is a problem faced by developed countries, however, the complications of over-nutrition are increasing even in countries where hunger is endemic²⁷. In developing countries undergoing health or epidemiological transition, a malnutrition pattern is predominantly emerging that is characterized by under-nutrition in children and ever-increasing obesity in adults^{28;29}, particularly adult females³⁰.

In Africa, being overweight and obese have traditional and cultural undertones³¹. In South Africa for instance, being obese is seen to reflect affluence and happiness in many regions of the population³². It was observed in the study that overweight or obesity in women reflected on a husband's ability to care for his wife and family. Overweight and obesity are also thought to reflect persons who are healthy and without HIV/AIDS³³. It is clear that these beliefs present complexities in the prevention and management of obesity in the African context.

2.1.5 Outcomes of diabetes mellitus

Nearly 50% of all people with Diabetes are unaware that they have the condition³⁴, meaning damage may have already occurred even at diagnosis. The risk of developing vascular complications of diabetes increases with increasing concentrations of hyperglycaemia³⁵. There is strong evidence from cohort studies of diabetic populations that in addition to duration of diabetes and metabolic control, blood pressure, cholesterol and ethnic/genetic factors are the main known determinants of vascular complications³⁶.

Microvascular complications which include retinopathy, nephropathy and neuropathy are more common and occur earlier in the course of the disease³⁷. Patients of African origin are thought to be at greater risk of developing these complications compared to Caucasians³⁸.

Macrovascular complications of diabetes such as cardiovascular disease are considered relatively less common in Africa despite a high prevalence of hypertension³⁹, although there is recent evidence to suggest increasing burden of cardiovascular disease on the continent⁴⁰. IDF estimates that, in 2015, five million people died from causes associated with diabetes, that is more than all the deaths from malaria, tuberculosis and HIV combined⁴¹.

Mortality associated with diabetes is significant in SSA, a systematic review found the 5-year mortality ranged from 4-57% in the region¹². This figure may have underestimated or overestimated the true value due to the bias of sampling only selected diagnosed diabetic patients accessing healthcare. It is not surprising that the complications of diabetes also account for the staggering cost of treating diabetes, estimated at over US \$670 billion dollars a year⁴².

2.2 Diabetic retinopathy

2.2.1 Diabetic retinopathy - A complication of Diabetes Mellitus

Diabetic eye disease comprises a group of eye conditions that affect people with diabetes, namely, diabetic retinopathy, diabetic macular edema (DME), cataract, and glaucoma⁴³. Retinopathy is the most common cause of vision loss among diabetics and is thought to evolve through several stages. Background retinopathy progresses to either DME or proliferative retinopathy (PDR) or a combination of the two⁴⁴. Both DME and PDR can independently lead to blindness hence they are sometimes collectively referred to as “sight threatening DR (STDR)”. Without treatment, 50% of patients with proliferative diabetic retinopathy (with retinal neovascularisation) will become blind within 5 years⁴⁵.

The challenge with DR is that it remains asymptomatic until it reaches advanced stages causing blindness in diabetic adults’ aged 20–74 years⁴⁶, making it the leading cause of blindness amongst working age adults. At diagnosis, 21–25% of type 2 patients and 9.5% of type 1 patients have some form of retinopathy⁴⁷. Recently, the DR barometer report found that 1 in 3 people with diabetes has diabetic retinopathy and 1 in 10 have STDR⁴⁸. Retinopathy is so characteristic of diabetes that its presence had previously been incorporated into the definition of NIDDM; ‘only hyperglycaemia of sufficient magnitude to be associated with retinopathy is classified as NIDDM whilst lower levels that are not associated with retinopathy are classified as impaired glucose tolerance⁴⁹.

The main risk factors for development of diabetic retinopathy are age, duration of diabetes and level of glycaemic control⁵⁰. The UK prospective diabetes study, a landmark study in our current understanding of the prevention and treatment of DR, showed that lack of control of hypertension and elevated cholesterol worsened the progression of DR³⁶.

2.2.2 Prevalence estimates of diabetic retinopathy

The importance of DR as a cause of blindness has increased due to the rise in DM prevalence, longevity and the decline in other preventable causes of blindness in developing countries⁵¹. DR is the fifth leading cause of blindness, globally affecting an estimated 1.8 billion people and is responsible for 4.8% of the blindness worldwide⁵². In recent years, due to better access to high quality cataract surgical services, DR is becoming a more significant cause of blindness⁵³.

The Diabcare Africa study carried out in 6 specialised diabetes centres found background retinopathy to be the leading eye complication [18%] followed by cataract [4%], amongst diabetic patients attending these centres⁵³. The prevalence of diabetic retinopathy varies from 16 to 77% depending on the duration of diabetes and glycaemic control⁵⁴. In west Africa for instance, the prevalence of DR was estimated to be 17.9% amongst diabetic population⁵⁵ whilst in South Africa 40.3% in rural regions was the prevalence⁵⁶. The latter study found that the complication rate among rural South Africans was high and that more than 1 in 10 diabetics had severe retinopathy requiring laser treatment. In 2012, a systematic review of the studies done in 21 African countries⁵⁷ reported the prevalence of any retinopathy in patients with diabetes to be between 30.2-31.6%. The review also found proliferative DR to be 0.9 - 1.3% and maculopathy 1.2-4.5%.

2.2.3 Prevention and treatment of DR- Results from landmark trials

The diabetes control and complications (DCCT) trial conclusively demonstrated the role of intensive glycaemic control in the prevention and progression of DR in diabetics. Study participants who kept their blood glucose level as close to normal were significantly less likely than those without optimal glucose control to develop diabetic retinopathy, as well as kidney and nerve diseases⁵⁸. Treatment for diabetic retinopathy is often delayed until it starts to progress to sight threatening DR⁵⁹. Treatment methods include photocoagulation, anti-VEGF/steroid injections, vitrectomy surgery or a combination of them. Laser photocoagulation has been shown to be a very effective treatment in the prevention of blindness from sight

threatening DR⁶⁰. The Diabetic retinopathy study⁶¹ (DRS) of 1976 found pan-retinal laser photocoagulation had reduced the 2-year risk of blindness by about 60%. Another trial followed, the ETDRS study which had over 3700 participants, demonstrated that effective treatment for diabetic retinopathy could reduce severe vision loss by 90%.

Focal laser therapy showed a 50% reduction in visual loss in those with DME⁶². Something of significance noted in that trial was that adverse effects of scatter photocoagulation on visual acuity and visual field were also observed. That proved the need for the inclusion of non-laser therapy in the overall management of DR.

2.2.4 Grading of Diabetic Retinopathy

Most classification systems for DR are based on landmark studies that tracked the appearance and progression of the disease⁶².

Table 1. Diabetic retinopathy disease severity scale based on the ETDRS classification system

Retinopathy stage	Findings on ophthalmoscopy	Management and review/referral timeframe
No apparent retinopathy	No abnormalities	In line with AOA, AAO, and JDC, OA recommends annual review
Minimal NPDR	Microaneurysms (MA) only	Review 6-12 months taking into consideration proximity of MA to fovea
Mild to moderate NPDR	More than just MA but less than severe NPDR. This may include: <ul style="list-style-type: none"> • dot haemorrhages • blot haemorrhages • cotton wool spots • intraretinal microvascular anomalies (eg venous beading) 	Refer or closely monitor Depending on level of DR present, 3-6 monthly or annually
Severe NPDR	Any of the following: <ul style="list-style-type: none"> • more than 20 intraretinal haemorrhages in each of 4 quadrants • definite venous beading in 2+ quadrants • prominent IRMA in 1+ quadrant AND no signs of proliferative retinopathy 	Ophthalmology referral
PDR	One of the following (or unexplained fall in VA) <ul style="list-style-type: none"> • neovascularisation • vitreous/pre-retinal haemorrhage 	Urgent ophthalmology referral (days – week)

2.3 Screening Programme for Diabetic Retinopathy

The effectiveness of treatment suggests that there is potential for a national screening programme to bring about a major reduction in blindness from retinopathy⁶³. Efficient identification of diabetic retinopathy is also cost-effective as numerous modelling studies demonstrate potential savings of hundreds of millions of dollars if an evaluation results in appropriate photocoagulation⁶⁴.

The gold standard for the detection and classification of diabetic retinopathy is stereoscopic color fundus photographs in 7 standard fields, as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group⁶². Although this technique is accurate and reproducible, it is labour intensive and requires skilled photographers; skilled photograph readers; and sophisticated photography equipment, film processing, and archiving⁶⁵. The turnaround time from acquisition of the data to interpretation can take weeks in clinical trials and therefore may not be appropriate in a busy screening clinic. In short, 7-field stereoscopic fundus photography technique serves well as the standard with which to compare other screening technologies.

Single-field fundus photography interpreted by trained readers is used to detect retinopathy that requires referral to an ophthalmologist; it is not used to comprehensively grade the level of retinopathy in the eye⁶⁶. It requires less time and less light (only one flash is required), and unlike photography of multiple fields, it may not require mydriasis in the majority of patients⁶⁷. One advantage of single-field fundus photography is the convenience to patients who do not have vision-threatening retinopathy. Therefore, the use of single-field photography may be a cost-effective way to use ophthalmic services because only patients with vision-threatening retinopathy are referred to an ophthalmologist.

2.4 Patient self-management of Diabetes Mellitus

Our health care system is designed to deliver acute, symptom driven care and therefore it is not surprising that physicians struggle to give the recommended level of DM care, especially in a busy office setting. Patients with chronic conditions such as diabetes self-manage their illness and are ultimately in control of their illness⁶⁸.

Regardless of what we as health professionals do or say, they control important self-management decisions such as what to eat, to exercise or not or even whether to be compliant with prescribed medication⁶⁹. This knowledge has led to the development of a new paradigm

of thinking, a so called “partnership” between patient and physician as opposed to traditional thinking where the doctor is regarded as the “expert”. Health systems in developed nations have started to adopt the view that chronic disease sufferers are their own principal caregivers and the health care worker is merely a consultant to support them in this role⁷⁰. Diabetes education has been considered an important part of clinical management for many decades and Interventions that involve patient collaboration are now found to be more effective than didactic interventions in improving glycemic control, weight, and lipid profiles⁶⁸.

Improved patient attitudes towards their disease and appreciation of the need for psychosocial wellness of the patient are needed in order to ensure better health outcomes for diabetics⁷¹. We have come a long way from the times when it was believed that just the acquisition of diabetes knowledge alone, was sufficient to ensure patient compliance, it has proven to be much more complicated than that.

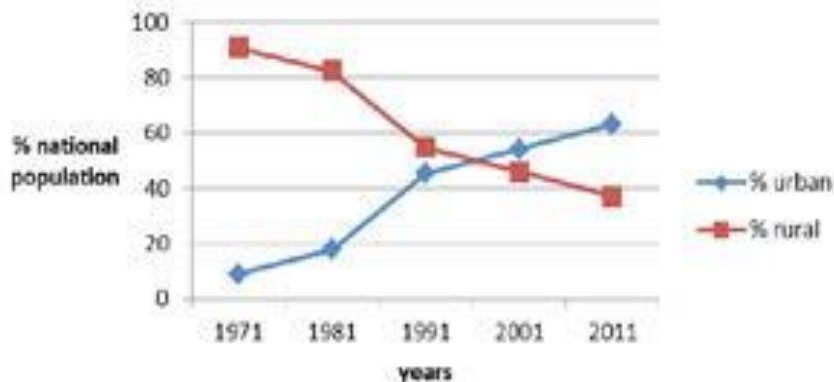
2.5 Situational analysis in Botswana

Botswana, with a population of just over 2 million, has developed from one of the least developed countries at independence in 1966 to an upper-middle income country mainly due to its prudent use and management of mineral resources and a stable democratic government system⁷². Despite this, Botswana continues to face multiple challenges such as high HIV prevalence rates with an estimated sero-prevalence of 37% amongst adults; high mortality rates among both women and children; persistent poverty and high unemployment⁷³.

Overall urbanization in Botswana has increased from 54 percent in 2001 to 64 percent in 2011. The major driver of urbanization in Botswana is the reclassification of its villages to an urban status, about 64 percent of the urban population resides in urban villages⁷⁴. This was a positive development for the nation because the new urban villages were then entitled to the allocation of better infrastructure and social services.

Figure 1. The national urban-rural tipping point between 1999 and 2000, when over half of the national population became classified as urban⁷⁴.

Urban-rural Population Distribution 1971-2011



There has not been a study to determine the number of diabetics living in the country but using WHO global estimates for a middle income country, the prevalence is conservatively estimated to be 4% of the population⁷⁵, which translates to 80 000/2 000 000. Using prevalence of DR rate of 20% (8 000 per million population) and among these, it is estimated 5% will be blind (400 per million population). The only population based study to date, looking at visual impairment nationally found DR to be the second leading cause of blindness (20%) after cataract in adult's aged 50 years and above⁷⁶.

Most of the prevalence data of DR from Botswana is limited to a few, mostly hospital/facility based studies. A survey in 2006 of diabetics attending a health facility in Botswana estimated the prevalence of retinopathy to be only 9.2% and was the third most common eye condition after refractive error and cataract⁷⁷. Another study completed in 2011, found the prevalence of DR to be 17.7% among the diabetics on the national screening register in Botswana⁷⁸.

2.5.1 Diabetic retinopathy screening service (DRSS) in Botswana

Retinopathy diagnosed early, followed closely and treated timeously with retinal laser therapy prevents blinding proliferative retinopathy and most importantly blindness⁷⁹. Therefore, both the IDF and WHO vision 2020 guidelines recommend early detection of DR by means of DR screening. The DRS Service in Botswana was developed by prevention of blindness program (PoB) in the ministry of health in October 2009 with the help of a UK based charity called Addenbrook's Abroad⁸⁰.

The screening was first done at Princes Marina hospital, a Referral facility in Gaborone until end of 2011 when it moved to Block 6 clinic. The DRSS went national in 2012 and included 3 additional screening sites, Donga Clinic in Francistown, Sekgoma Memorial Hospital in Serowe and Letsholathebe Hospital in Maun. Block 6 Clinic is still the designated “diabetic centre of excellence” and offers a comprehensive array of services for the overall management of diabetic patients. The DR screening is done by 2 trained ophthalmic nurses using a non-mydratic fundus camera. The nurses have also been trained to grade the pictures. However, attendance has been consistently low at the clinic and the “did not attend” (DNA) rate is estimated to be around 30% .⁸⁰

2.6 Conclusion

The above discussion has highlighted the significant burden of disease that diabetes and its most common ocular complication, Diabetic retinopathy, pose to our community. It is clear that the health systems particularly in developing nations such as Botswana, need to be better equipped to avoid the preventable blindness that occurs due to DR. Development of the screening programme is a step in the right direction but more data is needed in order for us to achieve maximum public health benefit from the population based programme.

2.7 Reference List

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SECTION C
JOURNAL READY ARTICLE

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The Prevalence and Determinants of Diabetic Retinopathy in Botswana: Findings from a Screening Programme

Nuru S. Omari

3.1 ABSTRACT

3.1.1 Background

The International Diabetes Federation estimates that the number of adults with diabetes in Africa will increase by 98% by the year 2030. The importance of diabetic retinopathy as a cause of blindness has increased because of longevity and a decline in the other preventable causes of blindness in developing countries. Retinopathy diagnosed early, followed closely, and treated timeously with retinal laser therapy, prevents blinding retinopathy. The objective of the study is to determine the prevalence of Diabetic Retinopathy, its determinants and the acceptability as well as accessibility of the screening service by patients.

3.1.2 Methods

The study is a cross-sectional study conducted at Gaborone diabetic retinopathy screening clinic. Convenience sampling was used where every eligible patient that arrived for DR screening and had consented was included in the study. Basic descriptive statistics of the study sample were reported and a multivariate analysis was performed with DR as the outcome of interest.

3.1.3 Results

A total of 220 participants attended the clinic between 12th of January and 6th of February 2015. The mean age of the participants was 55.96 (p=0.32) years and females comprised the majority 65.45% (n=144, p=0.33) of participants. A fifth of the participants (n=43, p=0.67) felt they had poor knowledge of diabetes and 25.91% (n=57, p=0.96) stated they did not understand the purpose of screening. Only 63.64% (n=140, p=0.46) reported to always being compliant with their medication and compliance did not differ significantly between those who had retinopathy and those who did not. Traditional medicine use was reported in 16.36% of the participants (n=36, p=0.33). Diabetic Retinopathy was found in 31.82% (n=70) of the population and of those, 3 participants (1.36%) had referable DR. Maculopathy was found in 21.82% (n=48) of participants. Increasing household number and years living with DM were the only variables found to have a significant association with development of diabetic retinopathy.

3.1.4 Conclusion

The prevalence of diabetic retinopathy has increased in our population compared to previous studies. The number of Diabetics attending the DR screening service in Gaborone has also increased but continuous diabetes health education cannot be over emphasized. Incorporation of local cultural values into the overall management of the disease is the best way to increase patient compliance.

3.2 Introduction

The World Health Organisation (WHO) estimates that there are more than 170 million people with diabetes mellitus (DM) worldwide and this figure is expected to rise to 366 million in 2030¹. The most rapid growth is expected in low and middle income countries amongst working age populations². The International Diabetes Federation (IDF) has estimated that the number of adults with DM in Africa will increase from 12.1 million to 23.9 million by the year 2030, a 98% increase. This is believed to be driven by the increase in urbanisation, sedentary lifestyles, obesity, population overgrowth and aging as well as successes in combating communicable diseases in the region¹. Sub-Saharan Africa (SSA), like the rest of the world, is experiencing an increasing prevalence of diabetes alongside other non-communicable diseases, a so called “double burden” of disease³.

Type 2 diabetes (T2DM) is the predominant form of diabetes in SSA⁴ and accounts for more than 90% of the cases, whilst type 1 diabetes mellitus, gestational diabetes and other specific types constitute less than 10%. Risk factors for the development of T2DM include obesity, ageing, and physical inactivity, often arising as a result of socioeconomic dynamics⁵. Recent evidence suggests that antiretroviral treatment has been shown to increase obesity and insulin resistance⁶, showing that communicable and non-communicable diseases are not separate entities as once considered.

Nearly 50% of all people with Diabetes are unaware that they have the condition⁷, meaning damage may have already occurred even at diagnosis. The risk of developing vascular complications of diabetes increases with increasing concentrations of hyperglycaemia and duration of disease⁸. There is strong evidence from cohort studies of diabetic populations that in addition to duration of diabetes and metabolic control; blood pressure, cholesterol and ethnic/genetic factors are the main known determinants of vascular complications⁹. Several

studies have shown that microvascular complications which include retinopathy, nephropathy and neuropathy are more common and occur earlier in the course of the disease¹⁰. It is reported that some cases of retinopathy can be seen as long as seven years before diagnosis of DM¹¹.

Diabetics of African origin are thought to be at greater risk of developing microvascular complications compared to Caucasians¹². Genetic predisposition may play a role, but most likely late diagnosis of diabetes, poor metabolic control and non-standardized diagnostic procedures may account for the difference from other populations¹³.

Diabetic retinopathy may be the most common microvascular complication of Diabetes. Diabetic eye disease comprises a group of eye conditions that affect people with diabetes, namely, diabetic retinopathy, diabetic macular edema (DME), cataract, and glaucoma¹⁴. It is thought to evolve through several stages: background retinopathy progresses to either DME or proliferative retinopathy (PDR) or a combination of the two¹⁵. Both DME and PDR can independently lead to blindness hence they are sometimes collectively referred to as “sight threatening DR (STDR)”.

Without treatment, it is reported that 50% of patients with proliferative retinopathy/retinal neovascularisation will become blind within 5 years¹⁶. In recent years, due to better access to high quality cataract surgical services, DR is becoming a more significant cause of blindness¹⁷. The effectiveness of photocoagulation therapy suggests that there is the potential for a national screening programme to bring about a major reduction in blindness from retinopathy. Early identification of diabetic retinopathy is also cost-effective; as previous modelling studies have demonstrated potential savings of millions of dollars if a patient evaluation results in appropriate photocoagulation¹⁸. Unfortunately, despite the consensus that examinations for the presence of diabetic retinopathy can reduce the risk of blindness, a large number of individuals with diabetes still do not receive such examinations.

DR screening programmes continue to have difficulty in attaining good attendance rates. The Botswana DRSS quotes their estimated “did not attend” (DNA) rate to be around 30%¹⁹. Evaluation of the screening programme in Botswana will therefore give us an understanding into the distribution and the determinants of DR. More importantly, this study will allow us to have better insight into patients’ attitudes and understanding of the screening programme and diabetes in as a whole.

3.3 Study Objectives

The primary objective of the study is to determine the prevalence of diabetic retinopathy (DR) and Sight Threatening DR in those that present for retinopathy screening in Gaborone, Botswana. The study sample at the primary clinic is presumed to be representative of the diabetic community.

The following objectives are outlined for the study:

1. To determine the prevalence of “any” DR in the patients screened at the centre.
2. To determine the proportion of “referable” DR amongst those that have retinopathy.
3. To assess how well the patients presenting for screening manage their diabetes.
4. To determine the accessibility of the screening service by the surrounding community.
5. To determine the level of awareness and acceptability of the screening service.
6. To explore the association between diabetic retinopathy and other predictor variables.

3.4 Methodology

3.4.1 Study design and setting

The study was a cross-sectional survey conducted in Gaborone at a primary healthcare clinic. The study ran for 5 weeks; from the 12th of January 2015 to the 6th of February 2015. Every eligible patient that arrived for DR screening services during that time and had consented was included in the study.

3.4.2 Population and recruitment

The study population were Type 1 and Type 2 diabetics above the age of 18years presenting to the eye clinic for purposes of DR screening only. The eye clinic is located within a primary healthcare clinic that has become the designated diabetes centre of excellence in Block 6 region of Gaborone. Some participants had been referred from surrounding health facilities specifically for DR screening.

Convenience sampling was used where consecutive patients were asked to participate in the study. Participation was voluntary and no form of incentive was provided. Explanation and consent was conducted in the patients' first language, Setswana. Eligible participants were recruited from the clinic waiting area, explanation of the study was given and consent was sought. The questionnaire was researcher administered to each participant in a private room in the eye clinic.

3.4.3 Screening for Diabetic Retinopathy in Botswana

The DR screening Service in Botswana was developed by the prevention of blindness program (PoB) in the ministry of health in October 2009 with the help of a UK based charity called Addenbrook's Abroad²³.

Block 6 Clinic in Gaborone is the designated "diabetic centre of excellence" and offers a comprehensive array of services for the overall management of diabetic patients. Visual Acuity (VA) in the better eye was recorded using Snellens' chart and the World Health Organization categories of visual impairment were used to define vision status (WHO, 2004). Normal vision is $>6/18$; visually impaired is between $6/18 - 3/60$ and blind is $<3/60$. Pinhole testing was used to ascertain *best corrected* VA as opposed to *presenting* VA.

This was done to exclude refractive error, particularly presbyopia, as a cause for visual impairment in this population. Mydriatic drops such as 1% tropicamide were then instilled into the eyes before retinal images were captured using a non-mydriatic digital fundus camera. The trained nurses performed both the screening as well as grading of the retinal images. Patients who have retinopathy that threatens their vision were referred to the ophthalmologist for further management.

3.4.4 Grading of Diabetic Retinopathy

The grading tool was based on the United Kingdom National Health Service (NHS) grading protocol but was revised by the Botswana Ministry of Health (MOH) prevention of blindness office. Most classification systems for DR are based on landmark studies that tracked the appearance and progression of the disease [ETDRS study]. The protocol grades retinopathy from R0 to R3 and maculopathy as a separate grade from M0 to M2 (see table below).

Participants' fundus were graded and placed into one of three categories:

1. "NO" retinopathy (grade R0/M0). Patient is asked to re-screen in 12 months.
2. "NON-REFERRABLE" retinopathy (R1-R2/M1). Patient is advised good glycaemic control and lifestyle modifications encouraged. Asked to re-screen earlier than 12 months.
3. "REFERRABLE" retinopathy ($>R2/M1$). Also known as sight threatening DR. Referral to ophthalmologist, may be immediate or within 4 weeks depending on the severity of disease.

The "ANY" retinopathy ($>R0$) category is the sum of referable and non-referable DR cases. This was done mainly for ease of statistical analysis, so that binary outcome can be obtained.

3.5 Data management and analysis

Data was collected by study personnel and recorded in participant questionnaires for entry into a Microsoft Excel database for storage. The data was cleaned using pivot tables in excel and exported to STATA version 14 (Stata Corp. College Station Texas) for analysis. Each participant was assigned a unique study number. The Microsoft Excel database only used the study number and not the name of participant therefore confidentiality was maintained at all times in the study. Basic descriptive statistics of the study sample were reported and a multivariate analysis was performed with DR as the outcome of interest.

The various risk factors collected from the participants were used to determine their association with the DR outcome. The level of significance for the estimates was set at 15% to increase the chances of seeing the associations between the different covariates.

Table 1- Retinopathy and maculopathy grading protocol for Botswana DRS Programme.

Adapted from NHS, UK Protocols revised by Botswana OPN and Office of Prevention of Blindness MO @SMH from 29th July to 2nd August 2013.

GRADE	CLINICAL FEATURES	CLASSIFICATION	SCREENING OUTCOME
RO	No Changes	No Retinopathy	Re-screen in 12months
MO	No Changes	No Maculopathy	Re-screen in 12months
R1	Microaneurysms, (MAs) Retinal Haemorrhages/exudates Venous loop	Background / Mild /Non –proliferative Retinopathy	Re-screen in 6 /12 to 12months
R2	Multiple deep, round or blot haemorrhage / Cotton wool spots / Venous beading/ Intra-microvascular abnormalities (IRMA)	Moderate or severe / Pre-proliferative Retinopathy	Re-screen in 3/12
M1 (if M1 is present, R1 <u>MUST</u> , be selected)	MA/Haemorrhages Within 1 DD from fovea	Maculopathy	Re-screen in 6 /12
M2 Referable	* R2 PLUS below *Exudates within 1DD of fovea /circinate or group of exudates within macula/retinal thickening within 1 DD	Maculopathy	Routine referral in 4/52 (4 weeks)
R3	New vessels on disc (NVD)/New vessels elsewhere (NVE)/ Pre-retinal or vitreous haemorrhage/pre-retinal fibrosis + retinal detachment	Proliferative Retinopathy	Urgent Referral in 2/52 (2 weeks)
Very Urgent	Sudden loss of vision / Retinal detachment	URGENT	Immediate Referral

3.6 Results

There were 227 eligible participants enrolled into the study. Every participant who was asked to participate in study agreed to take part. Seven “ungraded” participants were excluded because their retinas could not be viewed due to corneal opacities or cataract. The analysis used the remaining 220 participants [Table 2].

3.6.1 Demographic data

The mean age of the participants was 55.96 years (SD 13.8). Females comprised almost two-thirds of the participants, (n=144; 65.5%) compared to 34.55% (n=76) males. Most of the participants had only completed primary school (n=91; 41.4%) with 19.1% (n=42) having attained tertiary education. The majority of the participants were not employed (n=128; 58.2%) and the median years living with diabetes was 6 years (IQR 2-11.5years). Those who had retinopathy had been living with DM for 8.5 years compared with 5years for those without retinopathy

3.6.2 Vision and DR status

Almost all of the participants, (n=214; 97.3%) had normal vision. Five participants (2.3 %) were visually impaired and 1 participant was blind. Any Diabetic Retinopathy was found in 31.82% (n=70) of the population and of those, 3 participants (1.36%) had referable DR. Maculopathy was found in 21.82% (n=48) of participants, (n=15; 6.8%) 15 of those participants had maculopathy requiring referral to a specialist.

3.6.3 Patient self-management

Only 63.64% (n=140) reported to always be compliant with their medication and compliance did not differ significantly between those who had retinopathy and those who did not. The most popular medication regime used was oral hypoglycaemics (n=141; 64.1%), followed by combination of oral and insulin (n=48; 21.8%) then lastly only Insulin use in 25 of the participants (11.4%). Traditional medicine use was reported in 16.36% of the participants (n=36). The majority of the participants did not require a care taker (n=193; 87.7%) and those that did, their primary caretaker was their child and not a spouse.

3.6.4 Knowledge, accessibility and acceptability

A fifth of the participants (n=43) felt they had poor knowledge of diabetes, the rest (n=177; 80.5%), reported good to average knowledge of the disease. Half the participants (n=112; 50.9%) took 30 minutes or less to arrive at the clinic.

Only 10.9% of the participants' (n=24) took more than an hour to arrive at the clinic. A quarter of participants stated they did not understand the purpose of screening 25.91% (n=57).

3.6.5 Association between DR and predictor variables

Increasing number of people per household number and years living with DM were the only variables found to have a significant association with development of diabetic retinopathy. In our study, while holding everything constant, a 1 person increase in household number resulted in a 9.5% increase in risk of retinopathy in those with retinopathy compared with those without retinopathy (p=0.0120). Also, a 1-year increase in years living with DM results in an 8.7% increase in risk of retinopathy in those with retinopathy compared with those without retinopathy (P<0.05).

Table 2: Baseline characteristics of the sample by outcomes of retinopathy

Characteristic	All (n=220)	Any retinopathy (n=70)	Normal findings (n=150)	p-value
Age, mean (\pm SD)	56.0 (13.8)	57.3 (12.2)	55.3 (14.5)	0.322
Household number, median (IQR)	4 (3-6)	5 (3-6)	4 (3-6)	0.191
Marital status, n (%)				
Single/divorced/widow	111/220 (50.5)	36/70 (51.4)	75/150 (50.0)	0.844
Married/Domestic relationship	109/220 (49.5)	34/70 (48.6)	75/150 (50.0)	
Highest education level attained, n (%)				
Never/Primary education	117/220 (53.2)	38/70 (54.3)	79/150 (52.7)	0.823
Secondary/Tertiary education	103/220 (46.8)	32/70 (45.7)	71/150 (47.3)	
Employment status, n (%)				
Yes	92/220 (41.8)	29/70 (41.4)	63/150 (42.0)	0.936
No	128/220 (58.2)	41/70 (58.6)	87/150 (58.0)	
Years with Diabetes Mellitus, median (IQR)	6 (2-11.5)	8.5 (5-15)	5 (2-9)	<0.0001
Primary caretaker, n (%)				
Self	193/220 (87.7)	61/70 (87.1)	132/150 (88.0)	0.857
Child	27/220 (12.3)	9/70 (12.9)	18/150 (12.0)	
Knowledge of diabetes, n (%)				
Poor	43/220 (19.5)	14/70 (20.0%)	29/150 (19.3)	0.671
Average	94/220 (42.7)	27/70 (38.6%)	67/150 (44.7)	
Good	83/220 (37.7)	29/70 (41.4%)	54/150 (36.0)	
Medication, n (%)				
Diet/exercise	6/220 (2.7)	0	6/150 (4.0)	0.010
Oral medication	141/220 (64.1)	40/70 (57.1)	101/150 (67.3)	
Insulin	25/220 (11.4)	6/70 (8.6)	19/150 (12.7)	
Oral and injectable	48/220 (21.8)	24/70 (34.3)	24/150 (16.0)	
Compliance of diabetes management, n (%)				
Sometimes/Most of the time	80/220 (36.4)	23/70 (32.9)	57/150 (38.0)	0.460
Always	140/220 (63.6)	47/70 (67.1)	93/150 (62.0)	
Traditional medicine use, n (%)				
Yes	36/220 (16.4)	9/70 (12.9)	27/150 (18.0)	0.337
No	184/220 (83.6)	61/70 (87.1)	123/150 (82.0)	

Distance travelled to the clinic, n (%)				
<30 minutes	112/220 (50.9)	37/70 (52.9)	75/150 (50.0)	0.693
≥30 minutes	108/220 (49.1)	33/70 (47.1)	75/150 (50.0)	
First screening, n (%)				
Yes	65/220 (29.5)	18/70 (25.7)	47/150 (31.3)	0.395
No	155/220 (70.5)	52/70 (74.3)	103/150 (68.7)	
Understanding of screening purpose, n (%)				
Yes	163/220 (74.1)	52/70 (74.3)	111/150 (74.0)	0.964
No	57/220 (25.9)	18/70 (25.7)	39/150 (26.0)	
Sex, n (%)				
Female	144/220 (65.5)	49/70 (70.0)	95/150 (63.3)	0.333
Male	76/220 (34.6)	21/70 (30.0)	55/150 (36.7)	
Visual acuity, n (%)				
Blind	1/220 (0.45)	1/70 (1.4)	0	0.432
Normal vision	214/220 (97.3)	67/70 (95.7)	147/150 (98.0)	
Visually impaired	5/220 (2.3)	2/70 (2.9)	3/150 (2.0)	

3.7 Discussion

Our study found that almost a third of the diabetics at the screening service had some form of DR. This is a relatively high prevalence compared to previous studies done in Botswana among even though the previous studies looked at the facility based diabetic population similar to our study. Our findings are in keeping with a systematic review²⁰ of the studies done in 21 African countries in 2012 where the prevalence of any retinopathy was found to be between 30.2-31.6% and STDR was found to be 0.9 - 1.3%. The reason for that may be that uptake of the screening service is improving hence a more accurate reflection of the true burden of disease.

The study findings showed that participant compliance with medication was not optimal. It is well known that patient compliance in chronic disease self-management such as diabetes is very poor, our findings showed only two thirds admitted to always take their medication. Yet - there is evidence for and reference to the fact that blood glucose measurements were seldom taken and medication doses/regimens seldom altered/amended at primary care level - so while patients report compliance their management may still be sub-optimal. In addition to that, a significant proportion of the participants admitted to traditional medicine use and that may be

a contributor in the poor compliance observed. The WHO estimates that In Africa, up to 80% of the population uses traditional medicine to help meet their health care needs²¹.

Information bias where participants withhold certain information for fear of judgment may underestimate the true figure. More studies are needed to see the actual effect and extent of traditional medicine use in diabetics of Botswana. It is not surprising that majority of the participants were taking oral medication, due to high prevalence of type 2 diabetes in the region. Interestingly, those with retinopathy were more likely to be taking a combination of oral and insulin therapy compared to those without retinopathy. This may also imply a more aggressive form of diabetes or more co-morbidity or co-existing risk factors, more advanced disease in general.

A significant proportion of the participants in this study felt they did not understand the purpose of DR screening for diabetic retinopathy. We used this variable as a proxy to measure acceptability of the screening service in this population. We are aware the limitation of selection bias in assessing acceptability in a population that has already accessed the health service. Ideally population based studies would have better answered this question and allowed us to better understand the possible barriers. Having said that, the information gained in our study does suggest that continued diabetes health education will be of use in our population. The information gathered in the study will also be valuable as a baseline for comparison in future studies.

Years of living with DM is a well-known and important determinant of development of DR. A longitudinal study reported that after 20 years of diabetes almost all patients with Type 1 DM developed retinopathy, while approximately two-third of the patients with Type 2 DM developed retinopathy irrespective of their blood sugar control²². Hence not surprising that it was significantly associated with development of Diabetic retinopathy. Age is also a commonly reported risk factor for development and progression of DR but in this study the association between age and retinopathy was not significant. Reasons for this might be due to relatively small sample size and the skewed age distribution which if adjusted for might have yielded different results.

Attendance rates could be improved at the clinic and the “did not attend” (DNA) percentage is estimated to be around 30%. In national population-based screening programmes, the desirable target uptake is 80% which is difficult to achieve²³. Recall systems need to be put into place to

ensure better attendance rates such as short message system (SMS) alerts and phone call reminders. Limitations of this study include use of researcher administered questionnaire as opposed to self-questionnaire.

This may have exposed the study to biases resulting from participants' fear of judgment hence less truthful responses. Another limitation may have been the use of a quantitative study design to look at patient's perspectives on diabetes and the screening programme. A qualitative study may have allowed deeper understanding of the patient issues; such a study may be planned in future.

3.8 Conclusion

Diabetic retinopathy is prevalent in our community; this study shows that the prevalence has increased from approximately 10-15% to 30% compared to studies in the past. The number of Diabetics attending the DR screening service in Gaborone has increased but more effort needs to be made to encourage diabetics to attend for screening and to return for subsequent visits. Continuous diabetes health education cannot be over emphasized and incorporation of local cultural values into the overall management of the disease is the best way to increase patient compliance.

3.9 References

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