UNIVERSITY OF CAPETOWN

Assessment of factors associated with diabetic retinopathy among diabetic patients in Zambia

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Dissertation submitted in partial fulfillment of the requirements for the degree

MASTER OF PUBLIC HEALTH in Community Eye Health

in the

School of Public Health and Family Medicine

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January 2018

PREAMBLE

1. Declaration

I, Kanasa Kabaso (KBSKAN001), hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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2. Acknowledgements

I would like to acknowledge the following people for their invaluable help and support in completing this thesis.

To my supervisor, Prof. Robert Geneau, thank you for your support and guidance through every step of this dissertation.

To my co-supervisor, Prof. Paul Courtright, thank you for your support and insight during the conceptualization of this dissertation.

To Prof Collin Cook, Head of the Division of Ophthalmology at The University of Cape Town, thank you for your valuable comments on this thesis.

To Dr. Kamona Nkanza , Consultant Ophthalmologist, East Surrey and Sussex Health Care Trust, thank you for opening my eyes to the importance of preventing avoidable blindness, for your invaluable encouragement and paving a way for me to pursue this career path.

Finally, I must express my very profound gratitude to my parents, my husband my children and my friend Claire Engelbrecht for their unfailing support and continuous encouragement through the process of researching and writing this thesis. I would not have been able to accomplish this without them. Thank you.

3. Thesis abstract

Background: Diabetes Mellitus is an emerging public health problem in Africa. Evidence suggests that globalization, rapid urbanization and a nutritional transition have led to the rise in the prevalence of diabetes mellitus in Africa. Diabetic retinopathy is a common complication of diabetes mellitus that causes visual impairment and subsequent blindness. Early detection and prompt treatment can prevent blindness in up to 90% of patients. The common risk factors for diabetic retinopathy include hypertension, hyperglycemia and long duration of diabetes. Other risk factors include obesity, hyperlipidemia, smoking, puberty and pregnancy. There is limited data on diabetic retinopathy and its associated risk factors in Zambia. An understanding of these factors would help in the effective management of diabetic retinopathy.

Methods: A secondary data analysis of data obtained from a hospital-based cross-sectional study of diabetic patients attending diabetic clinics in the Copperbelt Province in Zambia was carried out. All diabetic patients that attended the retinopathy-screening program between April 2012 and September 2012 were eligible for the primary study. The secondary data analysis was restricted to patients 18 years and older. Data analysis was carried out by R version 3.3.1. The characteristics of the study population were summarized using descriptive statistics. Univariate logistic regression analysis was used to select potential candidates for the multivariate regression model at p-value cutoff point

≤ 0.25 and variables of known clinical relevance were also included in the multivariable analysis. The final model fitness was checked using Hosmer and Lemeshow chi-square test. Finally, statistical significance was tested at P-value <0.05.

Results: The prevalence of diabetic retinopathy was 19.4%. Multivariate analysis showed that the odds of diabetic retinopathy were significantly associated with age (OR =1.05: 95%CI; 1.03-1.06), duration (OR=1.39: 95%CI; 1.27-1.52), weight (OR =0.98: 95%CI; 0.97-0.98), blood glucose (OR =1.04: 95CI; 1.02-1.07) and systolic blood pressure (OR = 1.01: 95CI; 1.00-1.02).

Conclusion: Duration of diabetes, age, systolic blood pressure, weight and blood glucose levels were significantly associated with diabetic retinopathy in this study. More comprehensive population screening strategies and treatment programs addressing these risk factors should be put in place.

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A. PROTOCOL

1.Purpose of the Study

1.1 Study aim

To investigate the factors related to diabetic retinopathy among diabetic patients in Zambia.

1.2 Objectives

1. To identify the risk factors of diabetic retinopathy in Zambia.
2. To investigate the association between these risk factors and diabetic retinopathy.

2 Background

Worldwide, diabetes mellitus affects four times more people today than it did 30 years ago. (World Health Organization, 2016) Mathers and Loncar (2006) projected that by 2030 diabetes will be the seventh largest global cause of death worldwide. Diabetes and its complications have long been considered a problem of the industrialized countries. However, with the rising middle class and adoption of western lifestyle in Africa, the International Diabetes Foundation projects that the number of adults with diabetes mellitus in Africa will almost double by 2035 to reach 41·5 million. (Guariguata et al., 2014) This was supported by Boutayeb and Boutayeb (2005) who showed that non-communicable diseases are becoming more prevalent in Africa and adding to the disease burden that in the past were primarily caused by infectious diseases. A study done in Malawi showed that the prevalence of diabetes increased from less than 1.0% in the

1960s to 5.6% in 2009. (Msyamboza, Mvula & Kathyola, 2014) With the rise in diabetic cases it follows that there will be a rise in diabetic complications like diabetic retinopathy.

A systematic review of diabetic retinopathy and maculopathy in Africa found a wide range of prevalence estimates for diabetic retinopathy that depended on whether the study was population-based or clinic-based. In population-based studies, the prevalence rates for diabetic retinopathy ranged from 30.2% to 31.6%. In diabetic clinic-based studies, the reported prevalence rates for diabetic retinopathy ranged from 7.0% to 62.4%. (Burgess et al., 2013) A recent population based survey in Tanzania found the prevalence of diabetic retinopathy among diabetics to be 27.9%. (Cleland et al., 2016) The most common form of retinopathy was background diabetic retinopathy (19.1%), followed by maculopathy (16.1%), pre-proliferative (6%) and lastly proliferative diabetic retinopathy (2.9%). In comparison, the overall prevalence of diabetic retinopathy was higher in a population-based study in Kenya, which found the prevalence of diabetic retinopathy to be 35.9%. (Mathenge et al., 2014) However because of selection bias these studies cannot be generalized outside their context. A study in Ethiopia found that urban dwellers had a higher prevalence of diabetic retinopathy than rural dwellers. (Alemu et al., 2015)

The World Health Organization has declared diabetic retinopathy as the sixth leading cause of blindness, and as an important cause of avoidable blindness. (World Health Organization, 2016) Diabetic retinopathy is a microvascular

complication of both type 1 and type 2 diabetes mellitus and is an important cause of visual disability and blindness among diabetic patients. (Muaka & Longo-Mbenza, 2012). It is also the major cause of acquired vision loss in the economically productive age group worldwide. (Cheung & Wong, 2008) Diabetic retinopathy often has no early warning signs. However, early detection and treatment can prevent blindness in up to 70% of patients. (Mohamed, Gillies & Wong, 2007) Whereas diabetes in itself is a risk factor for vision loss there are other factors associated with diabetic retinopathy.

Risk factors of diabetic retinopathy

Kyari et al. (2014) demonstrated that diabetic patients in Nigeria are 3 times as likely to develop blindness as compared to the general population. A recent prospective cohort study done in Malawi, showed that the 2-year incidence of sight threatening diabetic retinopathy was 2.7% for diabetics who had no retinopathy, 27.3% for those with background retinopathy and 25% for those with pre-proliferative diabetic retinopathy. (Burgess et al., 2016)

Duration of diabetes

The Wisconsin Epidemiologic Study of Diabetic Retinopathy was an extensive study that followed people living with diabetes for 25 years in Wisconsin USA. It concluded that chances of having diabetic retinopathy increases with diabetes duration. It found that 67-98% of patients had diabetic retinopathy after 20 years.

(Klein et al., 2008) The study found that more than 80% of those with insulin dependent diabetes mellitus (type 1 diabetes) and more than 60% of non-insulin dependent diabetes mellitus (type 2 diabetes) would develop some degree of retinopathy after a 20-year history of diabetes. (Klein et al., 2008) However, a study in Kenya found that diabetic retinopathy occurs in younger diabetic patients compared to Western countries where diabetic retinopathy is associated with older diabetic patients. This was attributed to inadequate control of diabetes and hypertension in resource -poor nations. (Mathenge et al., 2014)

Glycemic control

Poor glycemic control of diabetes is associated with diabetic retinopathy. (Yau et al., 2012) Two large clinical trials found a relationship between glycemic control and the progression of diabetic retinopathy in both type 1 diabetes (Diabetes Control and Complications Trial Research group [DCCT], 1993) and type 2 diabetes. (UK Prospective Diabetes Study Group [UKPDS], 1998). The DCCT Research group found that intensive treatment in insulin-dependent diabetics reduced the incidence of diabetic retinopathy by 76% and the progression of diabetic retinopathy by 54%. The UKPDS showed that intensive treatment of diabetes reduced the development of any diabetic retinopathy by 25% in the intensive treatment group compared with the conventional treatment group. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy lower glycosylated hemoglobin was one of the factors found to be associated with improvement in diabetic retinopathy during the first four years of follow up. After

the 25 year follow up period it was demonstrated that people diagnosed most recently with a similar duration of diabetes had a lower prevalence of proliferative diabetic retinopathy independently of glycosylated hemoglobin level, blood pressure level, and presence of proteinuria. This was thought to be due to improvement in diabetes care over the study period. (Klein et al., 2008)

Hypertension

Blood pressure is an important risk factor for diabetic retinopathy. (Van Leiden et al., 2002) The UKPDS clinical trial demonstrated that hypertension is a risk factor for diabetic retinopathy in type 2 diabetes. Tight blood pressure control resulted in a 34% lower risk of progression of diabetic retinopathy in the study. (UK Prospective Diabetes Study Group, 1998) Hypertension very often coexists with diabetes. The incidence of hypertension is 3 times greater in people with Type 2 diabetes when compared to those without diabetes. (Rajalakshmi, Prathiba & Mohan, 2016) Hypertension is also a risk factor in type 1 diabetes. A prospective study showed that higher blood pressure is correlated to the early development of retinopathy in adolescents with type 1 diabetes, independent of other known risk factors. Both systolic and diastolic blood pressures contributed to the risk of retinopathy. (Gallego et al., 2008) In contrast, two large clinical trials the ACCORD study group (Buse et al., 2007) and the ADVANCE collaborative group (Patel et al., 2007) showed that intensive blood-pressure control did not reduce the rate of progression of diabetic retinopathy.

Lipids

The role of lipids in the pathogenesis of diabetic retinopathy is still disputed. The Early Treatment of Diabetic Retinopathy Study data showed that lowering lipid levels decreased the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy. (Chew et al., 1996)Findings in the Wisconsin Epidemiologic Study of Diabetic Retinopathy study agreed with this**,** when an association was found between higher total serum cholesterol and retinal hard exudates in insulin-dependent persons**.** (Moss, Klein & Klein, 1999) In the Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELD Study Investigators, 2005), among patients with type 2 diabetes, those treated with fenofibrate were less likely than controls to need laser treatment therefore had less severe retinopathy (5.2% vs 3.6%) Fenofibrate is used to treat high cholesterol and high triglyceride levels. However, there was no association found between total cholesterol and high density lipoproteincholesterol (HDL-cholesterol) with diabetic retinopathy or with hard exudates in the older onset age group not using insulin.(Klein et al., 1991) The ADVANCE study followed a cohort of 11140 patients with type 2 diabetes and concluded that HDL cholesterol is not an independent risk factor for development of diabetic retinopathy. (Morton et al 2012)

3 Study Rationale

Whilst a lot of research has been done on diabetic retinopathy in industrialized countries this is not the case in Africa, more so in Zambia. Zambia has a

population of 17.2 million. The International Diabetes Federation estimates the prevalence of diabetes to be 4.2% in Zambia. Therefore, there are approximately 722 400 people living with diabetes in Zambia. There is limited information on diabetic retinopathy in Zambia. Evidence suggests that with the growing middle class in Zambia, and adoption of a western lifestyle, diabetes cases are becoming more prevalent with increasing household socio-economic position (Bailey et al., 2016) This study aims at providing an understanding of the risk factors of diabetic retinopathy in Zambia, which will aid in developing effective diabetic retinopathy management programs. The study findings will also lay a foundation for advocacy, aimed at expanding screening programs for early detection and treatment of diabetic retinopathy and its associated risk factors across Zambia.

4 Methodology

4.1 Study design

This study will be a secondary data analysis of data obtained from a hospital-based cross sectional study, which was investigating the general awareness and prevalence of diabetic retinopathy among diabetic patients attending diabetic clinics in the Copperbelt Province in Zambia.

4.2 Study setting

The primary study was conducted in the Copperbelt Province of Zambia. The province has a total population of about 2,362,000. The major economic activity

in the Copperbelt is mining. Kitwe runs a new diabetic retinopathy screening programme that provides free screening for all diabetic patients in the province. Although the screening is restricted to Copperbelt Province, Kitwe Central hospital also receives referrals from across the country.

4.2.1 Inclusion criteria

All diabetic patients that attended the retinopathy screening centres between April 2012 and September 2012 were eligible for the primary study. The secondary data analysis will be restricted to patients 18 years and older.

4.2.2 Exclusion criteria

Diabetic patients who did not consent to be part of the study and those who did not attend the diabetic screening programme where excluded from the primary study.

4.3. Data collection

In the primary study, pre-coded interviewer-administered questionnaires were used to obtain information from the diabetic patients. Retinal images were reviewed by the researcher to determine the prevalence of diabetic retinopathy. Records from the screening programme were compiled and matched to records of referrals at Kitwe Central Hospital. Data for this secondary analysis will be taken from the interviewer –administered questionnaires and records from the

screening programme. (Appendices A and B). Variables that are used in this analysis are listed in Table A-1.

Table A-1: List of variables to be used for this secondary data analysis

Explanatory variables	Type
District	Categorical
Age	Continuous
Gender	Categorical
Duration of diabetes	Continuous
Blood glucose	Continuous
Systolic blood pressure	Continuous
Diastolic blood pressure	Continuous
BMI	Continuous
Intraocular pressure	Continuous
Seen by eye specialist	Categorical
Type of diabetes	Categorical

5. Data analysis

Statistical analysis will be carried out using R version 3.3.1. The characteristics of the study population will be summarized using descriptive statistics. Continuous variables will be described using means with standard deviations or medians with interquartile ranges depending on the data distribution, whilst categorical variables will be described using absolute numbers and percentages.

Analysis will include the use of Rank-sum and Kruskal–Wallis tests for continuous variables and chi-squared and Fischer tests for categorical variables. This will be done to determine if there are significant differences between different groups. Correlation between variables will be investigated and evaluated by use of scatter plots and frequency tables.

5.1 Model building

The primary outcome variable which is diabetic retinopathy will be treated as a binary variable; presence of any form of diabetic retinopathy versus absence of diabetic retinopathy. A logistic regression model will be used to identify predictors of diabetic retinopathy with variables being included if they are known to be risk factors for diabetic retinopathy as shown by existing literature or if a statistically significant association was found during univariate analysis. The odds of having diabetic retinopathy will be reported with 95% confidence intervals (CI) and a P-value of <0.05 will be considered to indicate statistical significance.

6. Potential Risks and Discomfort

There will not be any direct involvement with participants in this study as it is a secondary data analysis and therefore it presents minimal risk to participants.

7. Potential Benefits

The knowledge obtained from the study will provide further understanding of the risk factors of diabetic retinopathy in Zambia, which will aid in developing effective diabetic retinopathy management programs. The study findings will also lay a foundation for advocacy, aimed at expanding screening programs for early detection and treatment of diabetic retinopathy and its associated risk factors across Zambia.

8. Ethical considerations

Ethical approval for the primary study was obtained from relevant local ethical committees in the Copperbelt Province.

8.1 Informed consent

There will be no direct contact with the study participants therefore informed consent will not be obtained. The primary study obtained consent from the patients.

8.2 Privacy and confidentiality

Electronic data will be used in the study. The primary study removed all patient identifiers and replaced them with a unique code. This study does not have access to the key for the codes. Data will be entered and stored on password secured databases.

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B. STRUCTURED LITERATURE REVIEW

1.Introduction and objectives of this literature review

Diabetes is on the rise globally. The number of adults living with diabetes has increased worldwide from an estimated 108 million in 1980 to 422 million in 2014. (World Health Organization, 2016) It is projected that by 2030 diabetes will be the seventh largest global cause of death worldwide. (Mathers & Loncar, 2006) Low and middle-income countries have seen a disproportionate increase in diabetes cases compared to high-income countries. (World Health Organization, 2016) The prevalence of diabetes in Africa increased from 3·1% in 1980 to 7·1% in 2014, which is a 129·0% increase. (Allen, 2017) Globalization, rapid urbanization and changing food environments are the driving influences that have led to an increase in the risk and prevalence of diabetes and other non-communicable diseases (NCDs) in Africa. (Shaw, Sicree & Zimmet, 2010)

At present, poor health systems in Africa struggle to cope with infectious diseases and now face the added burden of an increasing prevalence of NCDs like diabetes. The health systems in African countries are unable to manage the current burden of diabetes and its complications. Apart from lack of equipment and drugs for treatment, health care providers were found to have insufficient knowledge on managing diabetes and its complications. (Atun et al., 2017)

The rise in diabetic cases inevitably means there will also be a rise in diabetic complications like diabetic retinopathy. Diabetic retinopathy has been declared

as the sixth leading cause of blindness, and as an important cause of avoidable blindness. (World Health Organization, 2016) Diabetic retinopathy (DR) is the leading cause of blindness among working-aged adults globally. (Kobrin Klein, 2007) Diabetic retinopathy is a microvascular complication of both type 1 and type 2 diabetes and is an important cause of visual disability and blindness among diabetic patients. (Muaka & Longo-Mbenza, 2012) Diabetic retinopathy often has no early warning signs. However, early detection and treatment can prevent blindness in up to 70% of patients. (Mohamed, Gillies & Wong, 2007)

This dissertation investigates the risk factors of diabetic retinopathy among a sample of diabetic patients in Zambia. It further quantifies the association of the risk factors to diabetic retinopathy. To inform this research, the objectives of the literature review are

- To describe the natural history of diabetic retinopathy.
- To provide an overview of the prevalence of diabetic retinopathy.
- To describe the progression of diabetic retinopathy.
- To describe existing evidence on factors associated with diabetic retinopathy.

2. Search methods

Pubmed, and Google Scholar were the search engines used to locate literature for this review. The search was restricted to English language publications, with no restriction applied with reference to time period or study design. Titles and

abstracts of resulting articles were reviewed and references of included studies and existing reviews were searched.

Publications available through August 2017 were included in this review. Search strategies using MESH terms and free language are listed in box 1.

Publications were included if:

- The study population had either type 1 or type 2 diabetes
- The study participants had risk factors for diabetic retinopathy
- The outcome of interest was diabetic retinopathy

Box 1: Search strategy

Diabetes: Diabetic retinopathy, Proliferative diabetic retinopathy, diabetes mellitus

Epidemiology: Prevalence, incidence, occurrence, epidemiology

Risk: factors, risk factors

Africa: Sub-Saharan Africa

3. Summary of Literature Review

3.1 Natural history of diabetic retinopathy

Diabetic retinopathy is divided into two main forms: nonproliferative and proliferative. The early stages of diabetic retinopathy are mild nonproliferative abnormalities, which are characterized by increased vascular permeability. The disease then progresses to moderate and severe nonproliferative diabetic retinopathy (NPDR), which is characterized by vascular closure. It further progresses to proliferative diabetic retinopathy (PDR), which is characterized by neovascularization on the retina and posterior surface of the vitreous. Macular edema is the thickening of the retina from leaky blood vessels. It can develop at all stages of retinopathy and if present it can be further classified as mild, moderate and severe. (Fong et al., 2004);(Klein et al., 1984)

3.2 Overall prevalence of diabetic retinopathy

A meta-analysis summarizing 35 studies carried out between 1980 - 2008 analyzed data from over 22000 people with diabetes. The study estimated a prevalence of any diabetic retinopathy of 34.6% and of vision-threatening diabetic retinopathy of 10.2% within the diabetes population. (Yau et al., 2012) However since data was pooled from various sources this could provide many potential sources of heterogeneity that could influence accuracy of the estimates.

Due to the wide range of methods used in determining diabetes status in different studies an overestimation of diabetes prevalence rates could have resulted.

It was estimated that in 2010 out of 32.4 million blind and 191 million visually impaired people, 0.8 million were blind and 3.7 million were visually impaired because of diabetic retinopathy. This represented a 27% increase in number of blind people and a 64% increase in the number of visually impaired people due to diabetic retinopathy compared to 1990 global estimates. Age-standardized prevalence of diabetic retinopathy-related blindness and visual impairment was found to be higher in Africa and South Asia. (Leasher et al., 2016)

A systematic review of diabetic retinopathy and maculopathy in Africa found a wide range of prevalence estimates for diabetic retinopathy that depended on whether the study was population-based or clinic-based. In population-based studies, the prevalence estimates for diabetic retinopathy among people with diabetes was found to be between 30.2% and 31.6%. In diabetes clinic-based surveys, the prevalence estimates for diabetic retinopathy ranged from 7.0 to 62.4%. (Burgess et al., 2013) However, the studies varied substantially in classification of retinopathy and methods used to ascertain the diagnosis. There is a paucity of population-based studies in Africa as large epidemiological studies are expensive. The majority of studies on diabetic retinopathy were hospital based. In hospital-based studies selection bias is a major issue and therefore need to be generalized with caution. (Burgess et al., 2013)

3.3 Sight-threatening diabetic retinopathy

A cross-sectional study in Malawi found the prevalence of sight threatening diabetic retinopathy to be 19.7% (14.7-24.6%) among type 2 diabetic patients and 18.8% (5.2-32.2%) among type 1 diabetic patients. (Glover et al., 2012) This is in contrast to a study conducted in the U.K that found a prevalence of sight threatening diabetic retinopathy in type 2 diabetic patients to be much lower at 6.0%. However, the prevalence of sight-threatening diabetic retinopathy in type 1 diabetic patients was 16.4% which is similar to the prevalence found in Malawi. The differences could be due to different methods in assessing diabetic retinopathy and variation in skills and knowledge to diagnose diabetic retinopathy. (Younis et al., 2002)

3.4 Progression

A systematic literature review and meta-analysis of prospective studies carried out between1975 - 2008 assessed the rates of progression of diabetic retinopathy to proliferative diabetic retinopathy (PDR) and/or severe visual loss (SVL). The study showed that the overall incidence of PDR and SVL observed in studies after 1985 (2.6% for PDR and 3.2% for SVL at 4 years) were considerably lower than rates observed before 1985 (19.5% for PDR and 9.7% for SVL at 4 years). (Wong et al., 2009) This meta-analysis was carried out with studies from developed countries and shows that there is a decline in incidence of blindness due to diabetic retinopathy in developed countries attributed to

improvement in the management of diabetes. (Sabanayagam et al., 2016) However, the rates of progression of diabetic retinopathy in Africa are different. A recent 5-year cohort study in Malawi found the overall progression of diabetic retinopathy to be 48.4% for diabetic patients who did not have evidence of retinopathy at baseline. (Burgess et al., 2017) The study found the progression to sight-threatening diabetic retinopathy (STDR) for those with no diabetic retinopathy was 19.4%, which was 5 times higher in comparison to recent European studies which found estimates of progression to STDR from no diabetic retinopathy to be between 3.9% - 4.0% (Younis et al., 2003a; Younis et al., 2003b). Burgess et al., 2017 found the 5-year incidence of STDR for those with background retinopathy to be 81.3%, which is 3 times higher than European estimates of between 26.8%- 28.9%. (Younis et al., 2003a; Younis et al., 2003b)

3.5 Risk Factors

There are several risk factors for diabetic retinopathy. Longer duration of diabetes, poorer glycemic and blood pressure control are the main risk factors to be strongly associated with diabetic retinopathy. (Yau et al., 2012) Risk factors for diabetic retinopathy can be classified as modifiable and non-modifiable. The major modifiable risk factors are hyperglycemia, hypertension, obesity and hyperlipidemia. The non-modifiable risk factors include duration of diabetes, puberty and pregnancy. (Ting, Cheung & Wong, 2016)

3.5.1 Modifiable risk factors:

Hyperglycemia

Poor glycemic control of diabetes is associated with diabetic retinopathy. (Yau et al., 2012) Two large clinical trials found a relationship between glycemic control and the progression of diabetic retinopathy in both type 1 diabetes (Diabetes Control and Complications Trial (DCCT) Research Group, 1993) and type 2 diabetes (UK Prospective Diabetes Study (UKPDS) Group, 1998). In type 1 diabetes the DCCT Research group found that intensive therapy reduced the mean risk of developing diabetic retinopathy by 76% compared with conventional therapy. The study also found that intensive therapy slowed the progression of diabetic retinopathy by 54% and reduced the development of proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy by 47%. In type 2 diabetes the UKPDS showed that intensive treatment of diabetes reduced the development of any diabetic retinopathy by 25% in the intensive treatment group compared with the conventional treatment group. Davis (1998) supported this view that the effect of better glycemic control is important in preventing diabetic retinopathy and added that this extends across all ages, both diabetes types and all stages of retinopathy.

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) lower glycosylated hemoglobin was one of the factors found to be associated with improvement in diabetic retinopathy during the first four years of follow up. After the 25 year follow up period it was demonstrated that more recently diagnosed cohorts with a similar duration of diabetes had a lower prevalence of proliferative diabetic retinopathy independently of glycosylated hemoglobin level, blood

pressure level, and presence of proteinuria. This was thought to be due to improvement in diabetes care over the study period. (Klein et al., 2008)

Hypertension

Blood pressure is an important risk factor for diabetic retinopathy. (Van Leiden et al., 2002) Controlling hypertension has been shown to reduce the risk of developing diabetic retinopathy and slowing its progression. (UK Prospective Diabetes Study (UKPDS) Group, 1998) A prospective study showed that higher blood pressure is correlated to the early development of retinopathy in adolescents with type 1 diabetes, independent of other known risk factors. Both systolic and diastolic blood pressures contributed to the risk of retinopathy. (Gallego et al., 2008) In contrast, two large clinical trials showed that the effect of intensive blood-pressure control are smaller than initially anticipated in reducing macrovascular and microvascular complications of diabetes. (Buse & ACCORD Study Group, 2007); (Patel & ADVANCE Collaborative Group, 2007)

Hyperlipidemia

The role of lipids in the pathogenesis of diabetic retinopathy is still disputed. The Early Treatment of Diabetic Retinopathy Study data showed that lowering lipid levels decreased the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy. (Chew et al., 1996) Findings in the Wisconsin Epidemiologic Study of Diabetic Retinopathy study agreed with this**,** when an association was found between higher total serum cholesterol and retinal hard exudates in insulin-dependent persons. (Moss, Klein & Klein, 1999) In the

Fenofibrate Intervention and Event Lowering in Diabetes Study, patients with type 2 diabetes treated with fenofibrate were less likely than controls to need laser treatment. They therefore had less severe retinopathy although the mechanism for this was not related to plasma lipid concentrations. (FIELD Study Investigators, 2005) Fenofibrate is used to treat high cholesterol and high triglyceride levels. However, there was no association found between total cholesterol and high-density lipoprotein cholesterol (HDL-cholesterol) with diabetic retinopathy or with hard exudates in the older onset age group not using insulin. (Klein et al., 1991) The ADVANCE study followed a cohort of 11140 patients with type 2 diabetes and concluded that HDL cholesterol is not an independent risk factor for development of diabetic retinopathy. (Morton et al., 2012)

Obesity

There are conflicting results on the association of diabetic retinopathy and a high Body Mass Index (BMI). (Ting, Cheung & Wong, 2016) In the WESDR being underweight (BMI < 20kg/m^2) was associated with a high risk of severe diabetic retinopathy. (Klein, Klein & Moss, 1997; Klein et al., 1984) However, the Diabetes Incidence Study in Sweden found high BMI to be significantly associated with diabetic retinopathy. (Henricsson et al., 2003) Significant associations between high BMI and diabetic retinopathy were similarly reported in the DCCT and the WHO study. (Zhang et al., 2001) (Keen et al., 2001)

Smoking

There is controversy on the role smoking has on diabetic retinopathy. The largest population-based study on diabetic retinopathy found no relationship between smoking status and progression of diabetic retinopathy. (Klein et al., 1998) However, Mhlhauser (1996) found a significant association between smoking and retinopathy although the strength of the relationship varied depending on the statistical model used.

Non-modifiable risk factors:

Duration

The Wisconsin Epidemiologic Study of Diabetic Retinopathy was an extensive population-based study that followed people living with diabetes for 25 years in Wisconsin USA. Participants were divided into 3 groups.

Group 1: participants with insulin dependent diabetes mellitus (IDDM) when age at diagnosis was 30 or more.

Group 2: participants with insulin dependent diabetes mellitus (IDDM) when age at diagnosis was less than 30.

Group 3: participants with non-insulin dependent diabetes mellitus when age at diagnosis was less than 30 years.

The groups showed the following prevalence:

Group 1: The prevalence of diabetic retinopathy was 28.8% in participants who had diabetes for less than five years whilst it was 77.8% in participants who had diabetes for 15 years or more. Proliferative diabetic retinopathy was found in

2.0% of participants who had diabetes for less than five years and 15.5% of participants who had diabetes for 15 or more years.

Group 2: The prevalence of diabetic retinopathy was 17% in participants who had diabetes for less than five years whilst it was 97.5% in participants who had diabetes for 15 years more. Proliferative diabetic retinopathy was found in 1.2% of participants who had diabetes for less than ten years and in 67% of participants who had diabetes for 35 or more years.

Group 3: The prevalence of diabetic retinopathy among those with non-insulin dependent diabetes mellitus was 36% at diagnosis whilst proliferative retinopathy was present in 5% after 20 years of diabetes.

The importance of duration as a risk factor for the development of diabetic retinopathy has been confirmed in several other studies. (Yau et al., 2012);(Ding & Wong, 2012)

Puberty and Pregnancy

The stage of sexual development is associated with diabetic retinopathy. (Klein, Moss & Klein, 1990) Olsen et al. (2004) demonstrated this when they found that type 1 diabetic patients diagnosed after puberty experienced a shorter mean time to develop diabetic retinopathy than those diagnosed before puberty. Pregnancy was reported to be associated with progression of diabetic retinopathy. (Klein, Moss & Klein, 1990) However, Stalnikiewicz et al. (2010) showed that progression of diabetic retinopathy is low particularly if diabetic retinopathy was mild or absent at the beginning of the pregnancy.

4. Identification of gaps or needs for further research

Although there have been numerous epidemiological studies in high-income countries since the early 1980's, on the prevalence, incidence and risk factors of diabetic retinopathy, there are very few high-quality studies on the prevalence of diabetic retinopathy in Africa. (Klein et al., 1984; Yau et al., 2012) Differences in population characteristics warrant the importance of conducting high-quality local studies in Africa.

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C. MANUSCRIPT

Assessment of factors associated with Diabetic Retinopathy among diabetic patients in Zambia

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Conflict of interest: The author does not have any proprietary interests or conflicts of interest related to this submission.

Statement: This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

* The article meets the requirements set out in the Instructions for Authors for the Ophthalmic Epidemiology journal. As per the MPH dissertation guidelines, co-authors are not listed in the journal manuscript but their contributions are noted in the acknowledgments section of this dissertation. The Ophthalmic Epidemiology Instructions for Authors are included in Appendix D of the dissertation.

Abstract

Purpose: Diabetic retinopathy is an important cause of avoidable blindness. The factors associated with diabetic retinopathy among diabetic patients at Kitwe Central Hospital in Zambia were identified and assessed.

Methods: This was a secondary data analysis of data obtained from a hospital-based cross-sectional study of diabetic patients attending diabetic clinics in the Copperbelt Province in Zambia. All diabetic patients that attended the retinopathy-screening centres between April 2012 and September 2012 were eligible for the primary study. The secondary data analysis was restricted to patients 18 years and older. Data analysis was carried out by R version 3.3.1. The characteristics of the study population were summarized using descriptive statistics. Univariate logistic regression analysis was done to select potential candidates for the multivariate regression model at p-value cutoff point ≤ 0.25 and variables of known clinical relevance were also included in the multivariable analysis. The final model fitness was checked using Hosmer and Lemeshow chi-square test. Finally, statistical significance was tested at p-value <0.05.

Results: The prevalence of diabetic retinopathy was 19.4%. Multivariate analysis showed that the odds of diabetic retinopathy were significantly associated with age (OR =1.05:95%CI; 1.03-1.06), duration (OR=1.39:95%CI; 1.27-1.52, weight (OR =0.98:95%CI; 0.97-0.98,blood glucose (OR =1.04:95CI; 1.02-1.07), systolic blood pressure (OR = 1.01:95CI; 1.00-1.02)

Conclusion: This study highlighted the statistical significance of the duration of diabetes as well as some important modifiable risk factors for diabetic retinopathy

among a sample of diabetic patients in Zambia, such as weight, blood glucose and systolic blood pressure. More comprehensive population screening strategies and treatment programs addressing these risk factors should be put in place.

Introduction

Diabetes mellitus is on the increase globally but low and middle-income countries have seen a disproportionate rise in diabetes mellitus cases compared to high-income countries. The rise in diabetes mellitus cases has been attributed to the increasing incidence and prevalence of type 2 diabetes mellitus. Population growth, aging populations and urbanization with its associated changing lifestyles (reduced physical activity and increased obesity) have led to increases in type 2 diabetes mellitus.[1] It is projected that the number of adults with diabetes mellitus in Africa will almost double by 2035 to reach 41·5 million. [2]

Diabetic retinopathy is the most common microvascular complication of both type 1 and type 2 diabetes mellitus. The prevalence of diabetic retinopathy is closely associated with the upsurge in prevalence of diabetes mellitus and is the leading cause of blindness among the productive age group globally.[3, 4] In 2015, among the 216·6 million people found to have moderate or severe vision impairment globally, 2.6 million had diabetic retinopathy and it was projected that the number would increase to 3.2 million people by 2020.[5]

Most patients who develop diabetic retinopathy have no symptoms until the very late stages when it is too late for effective treatment.[6] However, early detection and treatment can prevent blindness in up to 70% of patients.[7] Screening and follow-up is crucial for the effective management of diabetic retinopathy. However, follow-up rates are often poor in Africa due to various reasons including the cost to patients, poor transportation and lack of knowledge of

services.[8] The high rates of undiagnosed diabetes mellitus show that existing screening practices are not effective.[9] Additional strategies like targeting modifiable risk factors are therefore necessary in curbing the incidence of diabetic retinopathy. Several observational and randomized studies have shown that optimal blood glucose and blood pressure control are essential intervention strategies for the prevention of diabetic retinopathy and for slowing its progression. [4]

In contrast to the large amount of research that has been done on diabetic retinopathy in industrialized countries, there is limited research on diabetic retinopathy in Africa and more so in Zambia. Given the paucity of data on diabetic retinopathy in Zambia this study examines its risk factors to provide a better understanding of the factors associated with the disease, which can in turn aid in developing effective prevention programs.

Methods

This study is a secondary data analysis of a hospital-based cross-sectional study that aimed to determine the prevalence of diabetic retinopathy among diabetic patients attending diabetic clinics in the Copperbelt province of Zambia as well as the factors associated with treatment compliance in that population. The province has a total population of about 2,362,000.

Every diabetic patient that attended the retinopathy-screening program between April 2012 and September 2012 was eligible for the primary study. Diabetic retinopathy was classified as background retinopathy, pre-proliferative or

proliferative diabetic retinopathy. This was based on retinal images that were examined by a grader. This secondary data analysis classifies diabetic retinopathy as present or absent. The analysis was restricted to patients 18 years and older. Patients who had bilateral cataract were excluded from the study.

Data collection

Data for this analysis came from a review of records from the diabetic retinopathy screening program and interviewer-administered questionnaires, which were used to obtain information from the diabetic patients in the primary study (see Appendix A and B). The data was entered into Microsoft excel.

Data analysis

Data was analyzed using R version 3.3.1. Descriptive statistics were used to summarise the characteristics of the study population. Categorical variables were described using frequencies and percentages whilst continuous variables were described using means with standard deviations. The primary outcome variable was diabetic retinopathy and was treated as a binary variable; presence of any form of diabetic retinopathy versus absence of diabetic retinopathy.
Univariate logistic regression analysis was carried out to investigate the unadjusted association between variables and the outcome. It was also used to identify potential predictors for the full model with cutoff point of P-value ≤ 0.25 . The variable smoking had over 50% of its values missing and was therefore not included in the model.

Multivariable logistic regression analysis was done to estimate the effect of the predictors on diabetic retinopathy. The model was built by purposeful selection of variables and compared by the likelihood ratio test. Interactions and confounders were checked by using change in beta coefficient with cutoff point beta change greater than 20%. The final model fitness was checked using Hosmer and Lemeshow chi- square test. Finally, statistical significance was tested at p-value <0.05.

Ethical considerations

This study was conducted after getting ethical approval from University of Cape Town Human Research Ethics Committee. The TDRC Ethics Review committee in Zambia had approved the primary study. There was no direct contact with the study participants therefore informed consent was not obtained. The primary study obtained consent from the patients. The study adheres to the guidelines of the Declaration of Helsinki.

Results

Socio demographic characteristics

Overall 2401 diabetic patients were included in this study. Of these, 2220 (92.5%) were between the ages of 40-79 years. The mean age for the diabetic patients was 55.8 years. The age range was between 18 and 92 years. The age category with the largest number of diabetic retinopathy cases was among the 40-59 years old - 261 (56.1%) followed by the 60-79 years old - 189 (40.6%). The

mean age for study participants with diabetic retinopathy was 57.2 years whilst the mean age for those who did not have diabetic retinopathy was 55.4 years. Among the males 261 (19.7%) had diabetic retinopathy, whilst 204 (18.9%) females had diabetic retinopathy. Kitwe had the highest proportion 141 (30.3%), of diabetic patients with diabetic retinopathy followed by Ndola with 119 (25.6%). Masaiti had the lowest number of patients with diabetic retinopathy 7 (1.5%). Among the 2401 diabetic patients, 1148 (47.8%) had a family history of diabetes and among those with a family history of diabetes 253 (22%) had diabetic retinopathy. (Table C-1)

Clinical and bio chemical characteristics of study subjects

The prevalence of diabetic retinopathy among study participants was 465 (19.4%). Three hundred and fifty (14.6%) had background diabetic retinopathy, 53 (2.2%) had pre-proliferative retinopathy and 62 (2.6%) had proliferative retinopathy. Of the diabetic patients with diabetic retinopathy 163 (35.1%) had type 2 diabetes mellitus while 58 (12.5%) had type 1 diabetes mellitus and 244 (52.5%) had unknown status. Among patients with diabetic retinopathy, 130 (28%) had lived with diabetes mellitus for 11- 15 years. Three hundred and sixteen (68%) of the diabetic patients with diabetic retinopathy used oral hypoglycemic agents, 108 (23.2%) used insulin, 27 (5.8%) used diet and 14 (3%)reported no treatment. Three hundred and eight (66.2%) diabetic retinopathy patients had a systolic blood pressure greater than 140mmhg and 244 (54.8%) had a diastolic blood pressure greater than 90mmhg.Two hundred and seven

(49.6%) of the diabetic patients with diabetic retinopathy had blood glucose levels above 11mmol/l. Pertaining to the Body Mass Index of patients with diabetic retinopathy, 165 (35.6%) were of normal weight, 169 (36.4%) were overweight, 103 (22.2%) were obese and 27 (5.8%) were underweight. The mean Body Mass Index for diabetic patients with diabetic retinopathy was 26.6 whilst the mean Body Mass Index for those who did not have retinopathy was 28.1. Seventeen (3.7%) of diabetic patients with diabetic retinopathy had a history of smoking whilst 71 (3.6%) of diabetic patients without diabetic retinopathy had a history of smoking. (Table C-1)

Table C-1: Demographic and clinical characteristics of study participants stratified by presence or absence of diabetic retinopathy

Characteristic	**No retinopathy N (%)**	**Any retinopathy N (%)**
Total	1936(80.6)	465(19.4)
Mean age (standard deviation)	55.4(10.9)	57.2(8.5)
Age		
<20	5 (0.3)	0 (0)
20-39	142 (7.3)	11 (2.4)
40-59	1054 (54.4)	261 (56.1)
60-79	716 (37)	189 (40.6)
>80	19 (1)	4 (0.9)
Gender		
Male	1062 (54.9)	261 (56.1)
Female	874 (45.1)	204 (43.9)
District		
Kalulushi	102 (5.3)	23 (4.9)
Kitwe	588 (30.7)	141 (30.3)
Konkola	117 (6.0)	31 (6.7)
Luanshya	171 (8.8)	35 (7.5)

Masaiti	26 (1.3)	7 (1.5)
Mufulira	240 (12.4)	45 (9.7)
Nchanga	256 (13.2)	64 (13.8)
Ndola	436 (22.5)	119 (25.6)
Type of treatment		
Nothing	105 (5.4)	14 (3.0)
Diet	197 (10.2)	27 (5.8)
OHA	1364 (70.5)	316 (68)
Insulin	269 (13.9)	108 (23.2)
Smoking status		
Non-smoker	895 (46.2)	211 (45.4)
Ex-smoker	51 (2.6)	16 (3.4)
Current smoker	20 (1.0)	1 (0.2)
Not specified	970 (50.1)	237 (51)
Type of diabetes		
Type 1	147 (7.6)	58 (12.5)
Type 2	794 (41.0)	163 (35.1)
Not specified	995 (51.4)	244 (52.5)
Systolic blood pressure		
<140	925 (47.8)	157 (33.8)
≥ 140	1010 (52.2)	308 (66.2)
Diastolic		
<90	1141 (58.9)	210 (45.2)
≥ 90	795 (41.1)	255 (54.8)
BMI		
Mean(standard deviation)	28.1(6.1)	26.6(5.4)
underweight	98 (5.1)	27 (5.8)
normal weight	489 (25.3)	165 (35.6)
overweight	728 (37.6)	169 (36.4)
obese	619 (32)	103 (22.2)
unspecified	3 (0.05)	0 (0)
Blood glucose		
< 11mmol/l	1120 (64.1)	210 (50.4)
≥ 11mmol/l	626 (35.9)	207 (49.6)

Duration of diabetes (years)				
≤ 5	1077	(55.6)	119	(25.6)
6-10	491	(25.4)	106	(22.8)
11-15	237	(12.2)	130	(28)
16-20	72	(3.7)	59	(12.7)
>20	59	(3.1)	51	(10.9)
Family history				
no	792	(40.9)	167	(35.9)
yes	895	(46.3)	253	(54.4)
don't know	248	(12.8)	45	(9.7)

Univariate logistic regression analysis showed that except for diastolic pressure, districts and the sex of the patient other predictors satisfied the p-value criteria of ≤0.25 and were potential candidates for the multivariable logistic regression analysis. (Table C-2)

Multivariate logistic regression revealed that age, duration, systolic blood pressure, weight and blood glucose were associated to diabetic retinopathy. (Table C-2)

When adjusted for duration of diabetes, systolic blood pressure, weight, blood glucose levels, type of treatment, family history of diabetes and type of diabetes, the odds of having diabetic retinopathy increased by 5% for each year increase in age (OR: 1.05; 95% CI: 1.03-1.06). When adjusted for systolic blood pressure, weight, age, blood glucose levels, family history type of diabetes and type of treatment, the odds of having diabetic retinopathy increase by 39% for each year increase in duration of diabetes. (OR: 1.39; 95% CI: 1.27-1.52). The odds of having diabetic retinopathy reduced by 2% for each increase in weight when adjusted for age, duration of diabetes, systolic blood

pressure, treatment type, family history, blood glucose and type of diabetes. When adjusted for age, duration of diabetes, systolic blood pressure, weight, type of treatment, family history of diabetes and type of diabetes, the odds of having diabetic retinopathy increased by 4% for each unit increase in random blood glucose level. The interaction between age and duration was statistically significant.

Table C-2: Logistic regression analysis for factors associated with diabetic retinopathy

	Univariate analysis			Multivariate analysis		
Potential risk factors	**OR**	**(95% CL)**	**p-value**	**OR**	**(95%CL)**	**p-value**
Age	1.02	(1.01-1.03)	0.001*	1.05	(1.03-1.06)	<0.001
Duration	1.11	(1.09-1.11)	<0.001*	1.39	(1.27-1.52)	<0.001
Systolic	1.01	(1.01-1.02)	<0.001*	1.01	(1.00-1.02)	<0.001
Diastolic	1.02	(1.01-1.02)	<0.001*	1.00	(0.99-1.01)	0.382
Weight	0.98	(0.97-0.99)	<0.001*	0.98	(0.97-0.98)	<0.001
Height	0.99	(0.99-1.00)	0.248	Not included		
BMI	0.94	(0.93-0.97)	<0.001*	Not included		
District				Not included		
Kitwe	0.87	(0.57-1.34)	0.507			
Konkola	1.10	(0.66-1.86)	0.719			
Luanshya	1.19	(0.74-1.93)	0.485			
Masaiti	2.22	(1.10-4.46)	0.025			
Mufulira	0.86	(0.54-1.38)	0.516			
Nchanga	0.93	(0.59-1.50)	0.772			
Ndola	1.18	(0.78-1.83)	0.439			
Gender						
Male	ref					
Female	0.99	(0.83-1.19)	0.951	0.9	(0.74-1.10)	0.298
Treatment type						

Nothing	ref					ref
Diet	0.98	(0.58-1.67)	0.929	0.92	(0.51-1.65)	0.773
Oral	1.25	(0.82-1.97)	0.319	1.02	(0.64-1.69)	0.924
Insulin	2.08	(1.32-3.37)	0.002	1.39	(0.81-2.45)	0.241
family history						
No	ref					ref
Yes	1.16	(0.96-1.40)	0.123	1.06	(0.86-1.31)	0.562
Don't know	1	(0.75-1.33)	0.995	0.92	(0.67-1.25)	0.603
Blood glucose	1.04	1.02-1.06	0.001*	1.04	1.02-1.07	<0.001
Diabetes type						
Type 1	ref					ref
Type 2	0.53	0.40-0.72	0.001*	0.7	0.47-1.05	0.083
Not specified	500	0.37-0.67	0.001*	0.63	0.43-0.91	0.013*
duration:age				0.99	0.99-1	<0.001

*Statistically significant at $P \leq 0.05$

Discussion

Diabetic retinopathy is an emerging public health problem in low and middle-income countries due to the rise of diabetes mellitus.[10] In this study, the prevalence of any diabetic retinopathy was 19.4%. This was comparable to the prevalence estimates of 20.5% found in a study that looked at diabetic patients over the age of 18 years in Egypt.[11] However, this study used slit lamp biomicroscopy to diagnose diabetic retinopathy. A systematic review of diabetic retinopathy and maculopathy in Africa reported the overall prevalence rates of diabetic retinopathy in diabetic clinic-based studies to be between 7.0% and 62.4%. [12] Only 9 out of 62 studies on diabetic retinopathy in Africa used retinal

photographs and 6 of the studies were conducted in South Africa. [12] A clinic-based study in Tanzania that used digital fundal images to diagnose diabetic retinopathy reported a prevalence estimate of 27.9%. [13] Variations in the quality of the health care system could account for the differences in the prevalence estimates. These studies however cannot be generalized outside their context due to selection bias.

Diabetic retinopathy is the main cause of acquired vision loss in the economically productive age group in developed countries.[14] This study revealed that diabetic retinopathy similarly affects the economically productive age group in Zambia. This therefore underscores the importance of understanding factors associated with diabetic retinopathy for its effective management.

Duration of diabetes was the risk factor that was most strongly associated with diabetic retinopathy in this study. The odds ratio for duration of diabetes increased significantly from the univariate to multivariate analysis. (Table C-2) The proportion of patients with diabetic retinopathy increased with increased duration of diabetes. These findings support previous studies that showed that the prevalence of diabetic retinopathy increases with duration of disease. [15,16] However, developing diabetes mellitus in low and middle-income countries causes a great financial burden on the family and the outcome is often poor with reduced life expectancy.[9] This was demonstrated in this study by the smaller percentage of patients with diabetic mellitus who had the longest duration of diabetes. This can be attributed to the competing risk of death. Age was found to be significantly associated with diabetic retinopathy. The effect of age on diabetic

retinopathy interacts with the effect brought about by duration of diabetes mellitus. Therefore, the older a diabetic patient is, the longer they have lived with diabetes mellitus and the more likely they are to have diabetic retinopathy.

The study did not find any statistically significant association between the gender of patients and diabetic retinopathy. This finding is comparable to other studies that did not find a statistically significant difference in the prevalence of diabetic retinopathy among males and females.[14]

The study findings suggested that more patients with diabetic retinopathy had type 2 diabetes mellitus than type 1 diabetes mellitus. In low-income countries, type 1 diabetes mellitus is associated with a low life expectancy due to poor health care, socioeconomic conditions and unavailability of medication.[17] Therefore patients with type 1 diabetes mellitus may not survive long enough to develop complications like diabetic retinopathy.

The association between systolic blood pressure and diabetic retinopathy was statistically significant in this study. The odds of having diabetic retinopathy increased by 1 % for every unit increase in systolic blood pressure, when adjusted for other variables. This is consistent with studies done in America that found a 10% excess risk of diabetic retinopathy for each 10mmhg increase in systolic blood pressure.[15]

This study found that random blood glucose levels were positively associated with diabetic retinopathy. For every unit increase in blood glucose the odds of having diabetic retinopathy increased by 4 %. This is consistent with intervention

studies that found that improved glycemic control delayed the onset and progression of diabetic retinopathy. [18,19]

Several studies have yielded inconclusive results on the association of obesity with diabetic retinopathy. In one study diabetic patients who were underweight were found to have an increased risk of developing diabetic retinopathy [20] whilst another study [21] demonstrated an association between a larger Body Mass Index and diabetic retinopathy. In this study there was a 2% reduction in the odds of getting diabetic retinopathy per kilogram increase in weight. The reason for this could be that in resource-limited environments, those with low weight may be more likely to be poor, have a concomitant disease and ultimately be more at risk to have a poor health outcomes. [9,22,23] The association of family history of diabetes mellitus and diabetic retinopathy was not statistically significant in this study.

There was a wide range of diabetic retinopathy prevalence by location among the study cohort (30% prevalence in Kitwe compared to 1.5% in Masaiti). The differences can be attributed to the larger size of the population in bigger cities like Kitwe or Ndola, which contributed more study patients compared to small towns like Masaiti.

The strengths of this study are the large sample size of diabetic patients and the fact that it was carried out in a healthcare setting with access to existing records. An additional strength was the study design, which made it possible to analyze the outcome and various risk factors.

A limitation in this study was selection bias. Since the Copperbelt Province is one of the most developed provinces in Zambia, it is not representative of the Zambian population and therefore the results of this study cannot be generalized. Random blood sugar, which is a less sensitive marker, was used as a measure for blood glucose control rather than glycosylated hemoglobin (HbA1c.) With the available data it was not possible to ascertain the duration of diabetes as opposed to the time since diagnosis or the diabetic retinopathy prevalence when only a small portion of diabetic patients attend clinical services and fewer see an ophthalmologist. An additional limitation is that this study could not infer causality.

Conclusion

In this study, duration of diabetes was strongly associated diabetic retinopathy on multivariate logistic regression. Targeting individuals with a longer duration of diabetes would therefore be an important strategy in the prevention and management of diabetic retinopathy. Other risk factors associated with diabetic retinopathy were age, systolic blood pressure, weight and blood glucose levels. This suggests that modifiable risk factors of diabetic retinopathy in the Zambian population are largely similar to those found in developed countries. Controlling these risk factors may reduce both the prevalence and impact of diabetic retinopathy, as is the case in developed countries.

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D. APPENDICES

APPENDIX A : Demographic and Diabetic History Questionnaire

Knowledge, practice, and awareness regarding diabetic retinopathy among patients in Copperbelt Province of Zambia

Patient name		
Clinic name		
Interviewer name		
Date of interview		

Changed form on April 5

#	Question	Responses	Coding
Demographic questions			
1	Patient identification number		
2	Age (in years)		
3	Sex	Male ☐ (1) Female ☐ (2)	
4	Education	Primary I ☐ (1) Seceondary II ☐ (2) Tertiary III ☐ (3)	
5	Marital status	Married ☐ (1) Single ☐ (2) Divorced ☐ (3) Widowed ☐ (4)	
6	Religion	Christian ☐ (1) Hindu ☐ (2) Muslim ☐ (3) Other ☐ (4)	
7	Number of persons living in the same home as you		
Diabetic history			
8	How long have you been coming to this diabetic clinic? (months)		
9	When was your diabetes first diagnosed? (number of months ago)		
10	What were the first symptoms that alerted you or your doctor that you had diabetes?	Frequent urine ☐ (1) Large water intake ☐ (2) Visual loss ☐ (3) Diabetic foot ☐ (4) Diabetic coma ☐ (5) Dry mouth ☐ (7) Others ☐ (6)	
11	Who made the initial diagnosis of diabetes?	Doctor ☐ (1) Nurse ☐ (2) Other health work ☐ (3)	

		Others ☐(4)	
12	Where was the first diagnosis done?	Tertiary Center ☐ (1) Secondary level ☐ (2) Primary level ☐ (3) District Hospital ☐ (4) (Health center) ☐ (5) (Health post) ☐ (6) Others ☐(7)	
Current understanding of eye disease due to diabetes			
13	What are the major consequences or disabilities that a person with diabetes can get? (tick all)	Diabetic foot ☐ (1) Amputation ☐ (2) Visual loss ☐ (3) Stroke ☐ (4) Heart disease ☐ (5) Kidney disease ☐ (6) Others ☐ (7)	
14	Do you have any of these consequences or disabilities right now? (tick all)	Diabetic foot ☐ (1) Amputation ☐ (2) Visual loss ☐ (3) Stroke ☐ (4) Heart disease ☐ (5) Kidney disease ☐ (6) Others ☐(7)	
15	Have you been provided any education on how to prevent disabilities due to diabetes?	Yes ☐ (1) No ☐ (2)	
16	If yes, did the education include information on eye disease? (if Q15 = No, leave blank)	Yes ☐ (1) No ☐ (2)	
17	Who provided the information on eye disease? (if Q15 = No, leave blank. Also, if Q16 = No, leave blank)	Doctor ☐ (1) Nurse ☐ (2) Other health work☐ (3) Others ☐(4)	
18	Can eye disease due to diabetes be treated?	Yes ☐ (1) No ☐ (2) I don`t Know ☐(3)	
19	Have you ever had an eye examination to detect if you have any eye problems due to diabetes?	Yes ☐ (1) No ☐ (2)	
20	If yes, where did you have the eye examination? If Q19 = No, leave blank	Kitwe CH ☐ (1) Ndola GH ☐ (2) Company hospital ☐(3) Other hospital ☐ (4) Health centre ☐ (5)	
21	When should a diabetic patient see an eye doctor	On diagnosis ☐ (1) When referred☐ (2) After visual loss☐ (3) Others ☐ (4)	
22	How frequently should a person with diabetes have an eye exam?		

APPENDIX B: EYE EXAMINATION FORM

DILATED EYE SCREENING

ID Number:……..	Mobile Number: …….
Name of Patient:…… ……..	Age Sex: Male ☐ Female ☐

From screening form : Date: …… Presenting Visual Acuity:

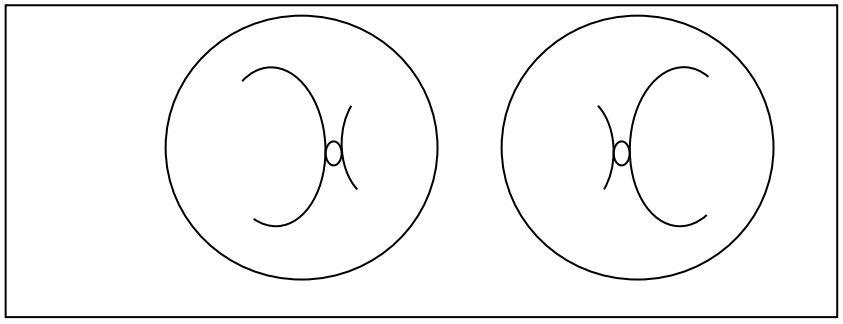
Blood pressure: ☐ Fasting Blood sugar: ☐ R/E ☐ L/E ☐

Digital Fundus photograph taken: ☐Y ☐N

Lens Opacity **R/E:** No Lens opacity interfering with photograph Yes Referred to Kitwe Eye Dept
L/E: No Lens opacity interfering with photograph Yes

Diabetic Retinopathy

R/E:	R 0 = No DR	M0 = No Mac
	R1 = BDR	`` MNR= Mac not referable
	R2 = Pre=proliferative DR	M1 = referable maculopathy
	R3 = Proliferative DR	
	P = Photocoagulation	OL/UG = other lesion/ungradable
L/E:	R 0 = No DR	M0 = No Mac
	R1 = BDR	MNR= Mac not referable
	R2 = Pre=proliferative DR	M1 = referable maculopathy
	R3 = Proliferative DR	
(NSC, 2008)	P = Photocoagulation	OL/UG = other lesion/ungradable



Referral to Kitwe Eye Dept for further assessment:

Yes: ☐ No: ☐

Name of grader: ……..

APPENDIX C: UCT Ethics Committee Approval

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 August 2017

HREC REF: 570/2017

Dr Robert Geneau
Division of Ophthalmology
H53, OMB

Dear Dr Geneau

PROJECT TITLE: ASSESSMENT OF FACTORS ASSOCIATED WITH DIABETIC RETINOPATHY AMONG DIABETIC PATIENTS IN ZAMBIA (MPH CANDIDATE - DR K KABASO)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

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 30 August 2018.

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.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Dr Kanasa Kabaso will also be involved in this study.

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), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix D : Journal submission guidelines

Ophthalmic Epidemiology

Instructions for Authors

All submissions should be submitted at http://mc.manuscriptcentral.com/nope
All submissions should be double spaced, with consecutively numbered pages. All abbreviations/acronyms must be defined at first use in the abstract, again at first use in the text and in each and every table or figure, regardless of seeming redundancy.

The following are the files need to make your online submission complete:

I. MANUSCRIPT FILE

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d) indicate who is the corresponding author and the corresponding contact

information (especially email),

e) financial support – list all financial support

f) list any proprietary interests or conflicts of interest for any and all authors related to this submission. “If none, please state: None of the following authors have any proprietary interests or conflicts of interest related to this submission:”; then list all the authors with no such interests. “None of the authors” suffices if no one has any such interests. Please err on the side of disclosure if it is unclear whether something is an interest or not, and please include relationships that may be perceived by others as a conflict of interest.

g) statement that this submission has not been published anywhere previously and that it is not simultaneously being considered for any other publication. Note: if the paper previously has been reviewed and rejected by another journal, please indicate so, and please indicate what criticisms were given and what changes have been made in response (as if you were revising and resubmitting to the original journal). We are open to accepting such papers if they have merit, and there is no need to hide this information.

2. Abstract – start on new page – not to exceed 250 words, define all abbreviations or acronyms used at first use, formatted into the following four sections:

a) Purpose

b) Methods

c) Results

d) Conclusion

3. Manuscript text – start on a new page. The text should not exceed 4,000 words. Define all abbreviations and acronyms at first use (even if previously defined in abstract). The text should be divided into the following 5 sections:

a) Introduction—give the rationale for why this manuscript is important

b) Materials and Methods – should include a statement regarding adherence to the guidelines of the Declaration of Helsinki as well as giving the name of the Institutional Review Board which granted approval or which indicated approval was not needed. Any waivers granted, such as HIPAA waivers or waiver of consent, should be mentioned. Whether patients consented to participate in the study should be mentioned; if not, the reason why not should be mentioned (e.g., Institutional Review Board waiver of consent)

c) Results—summarize the key and supportive results in a clear, crisp, straightforward manner.

d) Discussion—discuss what the key findings are, how it fits in with existing knowledge on the subject, and if there alternative explanations of the observations such as bias or random error. Please include a strengths and limitations paragraph, as well as a concluding paragraph summarizing the main items of knowledge that the paper has provided and relevant applications.

e) References – Please follow the directions in Section 4 below.

4. References - cite in the text as superscript by reference number, consecutively as they appear in the text, starting with 1. Prepare a numbered reference list. Only published and accepted (in press) articles can be cited. Abstracts should be cited parenthetically within the text as should any personal communication or unpublished data. Submitted articles are not citable, and should be referenced as unpublished data. Examples:

Journal:

Mohney BG, Robertson DM, Schomberg PJ. Second nonocular tumors in survivors of heritable retinoblastoma and prior radiation therapy. *Am J Ophthalmol*. 1998;126(2):269-277.

Book:

Raven JC, Court JH, Raven J. *Manual for Raven' Progressive Matrices and Vocabulary Scales*. London: H.K. Lewis & Co. Ltd., 1986.

The journal titles should be abbreviated.

For references with more than six authors, provide the names of the first three authors and then add et al.

II. **Tables and Figures**: Tables and figures should not be embedded in the text, but should be included as separate sheets or files. Each figure and table should

be a separate file uploaded into the system. A short descriptive title should appear above each table with a clear legend and any footnotes suitably identified below. All units must be included. Figures should be completely labeled, taking into account necessary size reduction.

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Confirm you are aware of copyright issues

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