PREVALENCE OF DIABETIC RETINOPATHY IN PATIENTS WITHTYPE 2 DIABETESMELLITUS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

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SM/PGM/05/13

A thesis submitted in partial fulfillment of the requirement of the degree of Master of Medicine in Internal Medicine, Moi University.

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DECLARATION

Declaration by candidate

This thesis is my original work and has not been presented before for an award of a degree or an academic credit in any university. No part of this thesis may be re-produced without the permission of the author and/or Moi University.

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This thesis has been submitted for consideration with our approval as university supervisors.

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DEDICATION

Dedicated to my late beloved father

ABSTRACT

Prevalence of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus at Moi Teaching and Referral Hospital, Eldoret, Kenya.

Background: Diabetic retinopathy (DR) is the 6thleading cause of global visual impairment; accounts for 5% of the 39 million causes of blindness occurring worldwide and is estimated to contribute 3% of blindness in Kenya. The risk of DR amongst patients with diabetes mellitus is increased by dyslipidemia, high glycated hemoglobin, hypertension, obesity and long duration of diabetes. This study addresses the gap in information on the magnitude of DR and its associated factors in patients with type 2 diabetes at Moi Teaching and Referral Hospital (MTRH).

Objectives: To determine the prevalence and severity of DR and its associated factors in patients with type 2 diabetes mellitus.

Methods: This cross sectional study was conducted amongst patients with type 2 diabetes mellitus in MTRH. Randomly selected participants underwent anthropometric, laboratory, visual acuity testing and ophthalomoscopy examination. Grading of DR was done using international clinical diabetic retinopathy severity scale. Data were analyzed using the SPSS and presented using frequency tables, cross tabulations, means, medians and standard deviation. A univariate and multivariate logistic regression model was used to assess associations of the variables with DR.

Results: Of the 329 participants enrolled, 187(57%) were female with a mean age of 56.8(10.99) years. 103(31%) had DR and 39(12%) had diabetic macula edema. Mild to moderate non proliferative diabetic retinopathy was the most prevalent grade at 79(25%). Fifty six percent (184) of participants had hypertension {133/80 (120/70-150/89)} mmHg. The median for the other assessed factors were as follows: duration of diabetes 5 (2-11) years, glycated hemoglobin 8.6 (7.2-11%), total cholesterol 4.5 (3.59-5.4) mmol/l and low density lipoprotein 2.97 (2.34-3.78) mmol/l. Duration of diabetes >10 years (OR 3.50(95% CI 1.82-6.77; p 0.0001), glycated hemoglobin > 7% (OR 5.34(95% CI 1.63-17.48; p 0.006), systolic hypertension >160 mmHg (OR 4.94(95% CI 1.97-12.39; p 0.001) and low density lipoprotein >3.3 mmol/l (OR 2.99(95% CI 1.45-6.16; p 0.003) were associated with increased risk of diabetic retinopathy while male gender and body mass index did not.

Conclusion: DR is a threat to sight in patients with type 2 diabetes in MTRH.

Recommendations: Strengthen the existing eye screening program to ensure every patient is screened early enough and optimize management of the modifiable factors namely high glycated hemoglobin, systolic hypertension and high low density lipoprotein.

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ACRONYMS

ACCORD – Action to Control Cardiovascular Risk in Diabetes

ADA - American Diabetic Association

BMI - Body Mass Index

BP - Blood Pressure

CARDS - Collaborative Atorvastatin Diabetes Study

CSME - Clinical Significant Macular Edema

DBP - Diastolic Blood Pressure

DM - Diabetes Mellitus

DR - Diabetic Retinopathy

ETDRS - Early Treatment Diabetic Retinopathy Study

HBIAC - Glycosylated Hemoglobin

HDL - High Density Lipoprotein

IDF – International Diabetes Federation

IREC - Institutional Research and Ethics Committee

LDL - Low Density Lipoprotein

MTRH - Moi Teaching and Referral Hospital

NDR - No Diabetic Retinopathy

SBP - Systolic Blood Pressure

PDR - ProliferativeDiabeticRetinopathy

T2D – Type 2 DiabetesMellitus

UKPDS - United Kingdom Prospective Diabetes Study

WHO - World Health Organization

DEFINITION OF KEY TERMS

Diabetes mellitus: A self-reported history of physician diagnosis or those who were on drug treatment for diabetes (insulin or oral hypoglycemic agents) or fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2 hour plasma glucose ≥ 11.1mmol/l (200mg/dl).

Patient with type 2 diabetes mellitus: A patient at the time of diagnosis is >30 years old and managed on oral hypoglycemic and/or insulin and/or diet; any patient regardless of age who is managed exclusively on oral hypoglycemic agents without insulin.

Hypertension: A self-reported history of physician diagnosis or subjects who were receiving drug treatment for hypertension or a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥ 90 mm Hg.

Diabetic retinopathy: Presence of one or more of following findings on fundoscopy will constitute diabetic retinopathy: micro-aneurysms, retinal hemorrhages, hard exudates, macular edema and ischemia, vitreous hemorrhage, traction retinal detachment and neo-vascular glaucoma

Diabetes mellitus duration: The time interval in years between the diabetes mellitus diagnosis date and the date of the present study.

Dyslipidemia:Presence of one or more of the lipoprotein being higher or equal to the 95^{th} percentile for total cholesterol, low density lipoprotein and triglyceride and lower than the 5^{th} percentile for higher density lipoprotein.

Direct ophthalmoscopy: Examination of the ocular fundus with a hand held instrument containing both a light source and exchangeable magnifying lenses; the examiner views

the fundus directly. It produces an upright or un-reversed image of approximately 15 times magnification.

Non-modifiable risk factors: These are factors that predispose one developing diabetic retinopathy but no interventions are available to tame them. They include genetic factors, gender and duration of diabetes. In this study male gender and duration of diabetes mellitus >5years are considered risk factors.

Modifiable risk factors: These are factors that predispose one developing diabetic retinopathy and various forms of intervention to treat them are available. They include hyperglycemia, hypertension, cigarette smoking and hypercholesterolemia.

Diabetic macula edema: Presence of hard exudates or micro-aneurysms and blot hemorrhages within one disc diameter of the foveal center.

CHAPTER ONE: INTRODUCTION

Diabetes Mellitus (DM) affects about 350 million people worldwide and results in considerable morbidity and mortality. The significant increase is in developing countries thought to be the result of population growth, ageing, obesity, and sedentary lifestyles. The International Diabetes Federation (IDF) has estimated the number of adults with DM in Africa will double in 20 years from 12 million in 2010 to 24 million in 2030(International diabetes federation, 2006).

Diabetes has many manifestations in the eye, of which cataracts and diabetic retinopathy (DR)are the most significant cause of visual impairment and blindness. People with diabetes are 25 times more likely than the general population to become blind. Cataract and DR are the second and sixth leading causes of global visual impairment respectively(Centre for disease control, 2003). Both are included in the list of nine target diseases of VISION 2020.

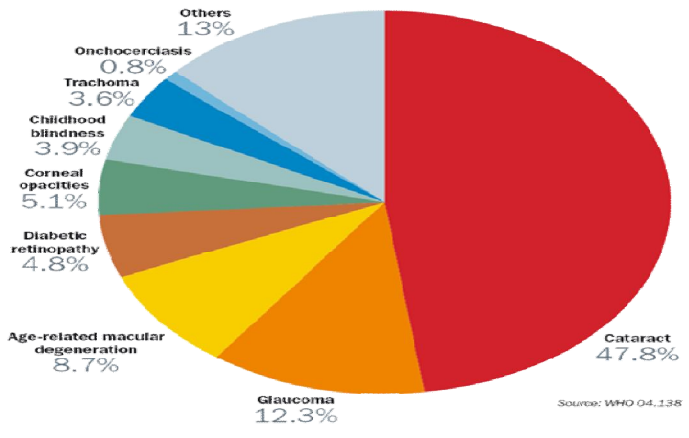

Figure 1: Global causes of blindness due to eye diseases, excluding refractive errors (WHO VISION 2020)

The world is facing an epidemic of DR, overloading the already inadequate eye care services in poorer countries. VISION 2020 protocol projects DR and the glaucoma as the 'emerging' causes of blindness in developing countries. In 1972, it was reported that there might be 10-15 million blind people globally. The World Health Organization (2011) estimates that over 285 million people in the world are visually impaired of whom 39 million are blind and 246 million have moderate to severe visual impairment. It is predicted that without extra intervention this number will raise to 75 million blind and 200 million visually impaired by the year 2020. Among the persons who are blind worldwide:

- 58% are aged >60 years
- 32% are ages 45 to 59 years
- 7% are ages 15 to 44 years
- 4% are aged<14 years.

About 80% of blindness is avoidable (preventable/curable) and about 90% of the world's blind occur in developing countries (World Health Organization, 2011). Cataract (48%) continues to be a major cause for global blindness, especially in the developing countries. Glaucoma (12%), age related macular degeneration (9%) and diabetic retinopathy (5%), along with cataract account for close to 75% of all blindness in the world(International diabetes federation, 2006). In developed countries, diabetic eye disease represents the leading cause of blindness in adults less than 75 years. World Health Organization (2002) released a world health report that showed more than 60% of people with type 2 diabetes mellitus will have evidence of DR. Visual impairment as a result of DR has a significant impact on patients' quality of life and can compromise their ability to manage successfully

their disease, which can in turn have a negative impact on the incidence of other diabetic complications and overall life expectancy.

Diabetic retinopathy is estimated to contribute about 3% of blindness in Kenya and almost 50% of diagnosed diabetes patients in Nairobi and almost 20% in rural central province had DR with the majority never having undergone any eye examination(Kenya society for the blind, 2008).

Diabetic retinopathy is a potentially blinding disease in which the threat to sight comes through two main routes: growth of new vessels leading to intraocular hemorrhage and possible retinal detachment with profound global sight loss, and localized damage to the macula / fovea of the eye with loss of central visual acuity. It is often asymptomatic and patients may not notice a change in their vision; however, the damage is always irreversible if not caught early.

The risk of DR to sight can be greatly reduced by good blood glucose and blood pressure control, effective screening and timely laser treatment. Since it is asymptomatic in its early stages, substantial barriers to screening and achieving regular eye examinations for people with diabetes include the belief that ‘nothing is wrong with my eyes’, not being told of the need for eye examinations and being too busy. In the developed world, it has been reported that about 36% of patients with type 2 diabetes mellitus have never had their eyes examined. In developing countries, diabetic eye care services are concentrated in the urban areas. There is limited data on magnitude of diabetes and its complications in the rural setup. Awareness about the available services and indeed, about diabetes and its complications is also lacking. Studies in urban Africa show high prevalence of DR with only 20% to 40% of patients with diabetes having had prior eye

examination by an ophthalmologist. It is postulated this figure could be higher in rural set up in Africa, given the limited access to health care.

The theoretical framework adopted for this study is derived from American Diabetes Association (ADA) recommendation for routine eye check-up among the diabetes patients in order to timely diagnose and treat DR and also the various studies that showed a strong relationship between DR and certain risk factors.

This study was conducted to determine the magnitude of diabetic retinopathy among type 2 diabetes mellitus patient in Moi Teaching and Referral Hospital and which specific risk factors cuts across those clients with this condition. The risk factors considered include hypertension, high glycated hemoglobin, dyslipidemia, duration of diabetes mellitus >5 years, high body mass index >30, increasing age and male gender.

The severity of the diabetic retinopathy was graded using the International clinical diabetic retinopathy disease severity scale that uses an evidence based approach based on results from the Early Treatment Diabetic Retinopathy Study (EDTRS) and Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) results.The results will help the hospital management for implementation of programs that would target prevention through early screening and diagnosis, risk reduction and treatment options for advanced cases.

CHAPTER TWO: LITERATURE REVIEW

Diabetes mellitus

Diabetes mellitus is defined as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion or insulin action or both(Centre for disease control, 2003)

Diagnosis of diabetes mellitus

According to the American Diabetes Association (Fong, et al,2003), the criterion for diagnosis of diabetes mellitus includes:

- Glycated Hemoglobin ≥6.5% or
- Fasting plasma glucose ≥126mg/dL (7.0mmol/L) or
- 2-hour plasma glucose ≥200mg/dL(11.1mmol/L) during an Oral Glucose Tolerance Test or
- A random plasma glucose ≥200 mg/dL(11.1mmol/L)

Impaired fasting glucose is defined as a fasting blood sugar of 5.6-6.9mmol/L (100-125mg/dL) whereas impaired glucose tolerance is defined as 2 hour plasma (postprandial) glucose of 7.8-11.0mmol/l

Incidence and prevalence of diabetes mellitus

In the study by Feltbower (2002),the incidence of type 2 diabetes mellitus has risen dramatically driven by longevity combined with sedentary lifestyles and increasing levels of obesity and Wild (2004) suggested that the most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age.

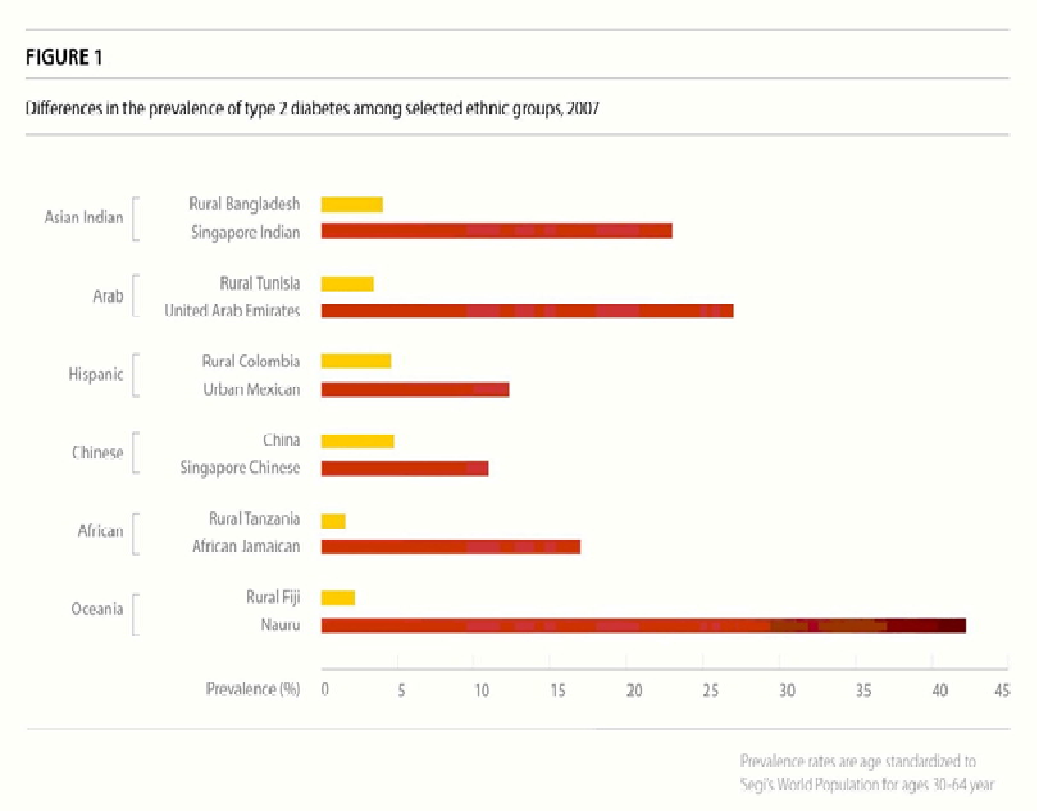

Figure 2: Differences in the prevalence of type 2 diabetes among selected ethnic groups (IDF diabetes atlas, 2006).

From figure 1, many of the differences between these rates reflect underlying behavioral, environmental and social risk factors, such as diet, level of obesity and physical activity.

The International Diabetes Federation (IDF) published data in 2006 which showed that diabetes affects about 250 million people worldwide, with 46% of all those affected in the 40-59 working age group. The new data predict that the total number of people living with diabetes worldwide will rise to 552 million by 2030 (International Diabetes Federation, 2006).

The number of type 2 diabetes mellitus is estimated to rise dramatically in the near future in most developing and intermediate societies, affecting particularly urbanizing societies and the middle-aged population(Kenya society for the blind, 2008). About 80% of the persons with diabetes live in the low and middle income countries. Most of these are between the ages of 45 to 65 years and they represent a very productive segment of the economy in these societies. Diabetes deaths are likely to increase by more than 50% in the next 10 years without urgent action. Seven out of the ten world's leading countries with highest number of people with diabetes are in developing countries, for instance, India has the highest population (95million living with diabetes). Africa has not been spared from this phenomenon of rapid increase in diabetes patients. About 10.4 million Africans have diabetes (3.1% of the adult population) and 24.2 million have glucose intolerance which can lead to diabetes. The prevalence of diabetes mellitus in Kenya is estimated at 3.3% with up to 50% being undiagnosed. Kenya is one of the six african countries with high prevalence of diabetes mellitus and about1.7 million Kenyans are living with diabetes(Kenya Diabetes Management and Information Center, 2014).Type 2 diabetes mellitus is the more prevalent, and kenyans are developing it younger than others in developed countries. The age of onset in Kenya is between 45 and 55 years, compared

with 64 years in developed countries. Kenyans are also at higher risk for crippling or life-threatening complications, because they report to health centers when the disease is advanced (East African News Paper, 2007).

Prevalence and causes of blindness

The World Health Organization (2011) estimates that 39 million people are blind worldwide, yet an estimated 80% of the blind suffer needlessly. More recently, following a review of available data by Watkins (2011), he estimated that there were about 40 million people (0.7%) who are blind worldwide and predicted an annual increase of about two million. Diabetic retinopathydevelops in more than 77% of patients with type 2 diabetes mellitus who survive over 20 years with the disease. It is generally known that Africa has a high rate of blindness. It has been estimated that approximately 1% of Africa's population is blind and a higher prevalence has been estimated for Sub-Saharan Africa(Oduor K., 2009). The most common causes of low vision and blindness among adults are cataract, corneal and retinal diseases. Millions could be cured because their blindness is caused by conditions that are easily treatable or preventable. With worldwide estimated39 million blind people, diabetic retinopathy emerges as the 4th leading cause of preventable blindness among adults aged 20-75 years accounting for approximately 5% of blindness and it remains a significant health problem worldwide as reported by the American Diabetes Association (Fong et al, 2003). While it is the number one cause of avoidable blindness for the working population in the industrialized world it is said to account for 5-10% of blindness in intermediate economies. In Africa it appears that at diagnosis, 21 to 25% of type 2 diabetes mellitus have diabetic retinopathy(Wea S, 2004). It does seem likely that blinding diabetic eye disease is now the fourth major cause of blindness worldwide after cataract, the glaucomas and trachoma. This change is due to

the reduction of blindness from corneal opacities, the aging population of the world and some improvement in health care systems in many developing countries.

Table 1: Causes, proportion and trends of blindness worldwide

Causes, Percentages and Trends of Global Blindness (Foster A, 2009)		
Cause	%	Trend
Cataract	50	Increasing
Refractive errors	10	
Glaucoma	10	
Diabetic retinopathy	5	
ARMD/and Other Diseases	10	Decreasing
Trachoma/ Infective Scars	12	
Onchocerciasis	2	
Vitamin A Deficiency	1	

Diabetic retinopathy is estimated to contribute about 3% of blindness in Kenya. In consecutive studies the situation for a major referral hospital in Nairobi and for diabetes programs in rural Kenya were examined with the following major results (extracts):

1. Urban national referral hospital (N = 601, patients attending the diabetes clinic): 49.8% had diabetic retinopathy; 82% had no previous eye examination and 48.6% of diabetic retinopathy patients needed some sort of treatment. 19.7% had blinding conditions (13.4% clinically significant macula edema, 6.3% proliferative diabetic retinopathy)

2. Rural clinics/hospitals (N = 410, patients attending the diabetes clinic): 18.3% had diabetic retinopathy; 4.9% had blinding conditions (4.5% clinically significant macula edema, 0.4% proliferative diabetic retinopathy)

3. Urban national referral hospital (N = 71, newly diagnosed diabetes patients attending diabetes clinic): 30.4% had diabetic retinopathy, 12.5% had blinding conditions (8.2% clinically significant macule edema, 4.3% proliferative diabetic retinopathy)

Njambi, et al(2012) estimated the prevalence of diabetic retinopathy at Embu provincial hospital at 41% hence these data provide evidence of diabetic retinopathy as an emerging problem for Kenya.

Improvements in diabetes care and earlier detection of the disease can reduce the incidence of visual impairment and blindness(Fong, et al, 2003). By the time of a clinical diagnosis of type 2 diabetes, some individuals already show evidence of diabetic retinopathy indicating diabetes may have been present for several years.

Risk factors for diabetic retinopathy

Long duration of diabetes, hyperglycemia, hypertension, dyslipidemia, obesity, proteinuria and low socioeconomic status play important role for development of diabetic retinopathy. Long duration of diabetes and inadequate glycemic control are most important(Diabetic retinopathygroup, 1993).

Risk factors for diabetic retinopathy are divided into two:

i) Non-modifiable: Genetic factors, male gender and duration of diabetes over 5 years.

In Wisconsin Epidemiologic Study of diabetic retinopathy (Early Treatment Diabetic Retinopathy Study Group, 1991) of those with an onset at 30 years of age (presumed to have type 2 diabetes mellitus) among the 40% who were using insulin 24% did not have any degree of diabetic retinopathy when the duration of diabetes mellitus was fewer than 5 years and then 53% developed some degree of diabetic retinopathy when the duration of diabetes was 15-20 years. In Africa, a longitudinal cohort study in Malawiby Mbanya, Sobngwi,(2003) estimated prevalence of diabetic retinopathy at 28.1% after mean diabetes duration 6.7 years, of whom 12.5% had proliferative diabetes retinopathy. In patients with diabetes mellitus with duration longer than five years, prevalence of diabetic retinopathy was 23.2% and proliferative diabetic retinopathy was 3.2%. In those with disease duration longer than 16 years, prevalence of diabetic retinopathy was 66.7% and proliferative diabetes retinopathy and blindness were 14.3%. These findings are similar to earlier reports (10-15 years old) where overall retinopathy prevalence in (mainly) adult type 2 diabetes mellitus patients varied from 15-56% (Ricardo, 2007) depending on the duration of diabetes and glycemic control. In Kenya, Njambi,et al, (2012) found duration of diabetes had a significant association with diabetic retinopathy.

ii) Modifiable: hyperglycemia, hypertension, cigarette smoking and dyslipidemia

a) Hyperglycemia

After a mean duration of follow-up of 10 years in the United Kingdom Prospective Diabetes Study (UKPDS) reduction of glycated hemoglobin from 63mmol/l (7.9%) to 53mmol/l (7.0%) was associated with a 25% risk reduction of micro vascular

complications(Matthews, Aldington, Holman, Kohner, 2004). Further confirmation of the value of good glycemic control in type 2 diabetes mellitus was obtained in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study where reduction of glycated hemoglobin from mean 58 to 46mmol/l was associated with reduced primary outcome (3-step increase on the ETDRS scale or development of proliferative retinopathy requiring photocoagulation or vitrectomy) from 10.2% to 6.5% and progression of retinopathy was reduced by 42%(Stratton, Adler, Matthews, Neil, Holman, 2006).

b) Hypertension

Blood pressure control plays an important role in prevention and management of diabetic retinopathy. The United Kingdom Prospective Diabetes Study(1998)showed that a reduction of mean systolic blood pressure from 154 to 144mmHg reduced micro aneurysm count at 4.5 years follow up, reduced hard exudates and cotton-wool spots at 7.5 years, and was associated with less need for photocoagulation and less deterioration of 2-step or more on the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy scale(ACCORD Study Group,2010 June).

c) Dyslipidemia

Lipid-lowering is another approach that may reduce the risk of progression of diabetic retinopathy, particularly macular edema and exudation. The possibility of an effect of statins has been investigated over the last 10 years with some encouraging results. For example, 2838 patients in Collaborative Atorvastatin Diabetes Study (CARDS) followed over a median follow-up of 3.9 years with atorvastatin 10mg daily, showed a trend to reduced laser therapy but no influence on diabetic retinopathy progression(Colhoun et al, 2004). Two large randomized controlled trials of fenofibrate have subsequently confirmed benefit in established retinopathy. First, in the Fenofibrate Intervention and Event

Lowering in Diabetes (FIELD) study (Keech et al, 2007)Fenofibrate (200 mg formulation /day) reduced the requirements for laser therapy (both macula and pan retinal/scatter laser)and prevented disease progression in patients with pre-existing diabetic retinopathy. These benefits did not appear to be related to changes in lipid levels as there were no reported clinically relevant differences in mean plasma high density lipoprotein cholesterol or triglyceride concentrations in those with or without laser treatment. Secondly, the Action to Control Cardiovascular Risk in Diabetes Eye study (ACCORD Study Group, 2010 June) showed a 40% reduction in the odds of having progression of retinopathy over four years in patients allocated to fenofibrate (160 mg formulation/day) in combination with a statin, compared to simvastatin alone. This occurred with an increase in high density lipoprotein-cholesterol and a decrease in the serum triglyceride level in the fenofibrate group, as compared with the placebo group, and being noted in the first year of treatment and maintained.

Ocular complications associated with diabetes mellitus

The ocular complication of diabetes may be specific to progression of the ocular disease or, more commonly, may be non-specific recognized associations of diabetes in the eye.

Table 2: Eye complications linked to diabetes mellitus

Specific	Non-specific
Retinal detachment	
Rubeosisiridis	
Cataract	Glaucoma
	Retinal vein occlusion/Optic disc swelling Optic neuropathy
Optic neuropathy	

Non-specific diabetes mellitusocular complications:

a) **Glaucoma** is defined as loss of vision due to raised intraocular pressure and occurs in two forms, primary or secondary. Primary glaucoma may present as acute glaucoma or chronic glaucoma. Patients with diabetes were previously thought to have a greater risk of developing primary chronic glaucoma with loss of visual field (side vision). However, more papers that are recent suggest that diabetes is not a greater risk factor, but simply that glaucoma was found more readily (Agrawalet al, 2003). Patients with proliferative diabetic retinopathy are at risk of developing secondary glaucoma, particularly neo-vascular (rubeotic) glaucoma.

b) **Retinal vein occlusion / Optic disc swelling**. Patients with diabetes are at higher risk of developing optic nerve disease due to vascular occlusion, which is distinct from diabetes-specific optic neuropathy and usually occurs in older patients with

type 2 diabetes mellitus and hypertension. This may be a form of ischemic optic neuropathy.

c) **Optic neuropathy**. Patients with diabetes may rarely experience optic neuropathy, which presents as swelling of the optic discs associated with gradual reduction in visual acuity.

Specific diabetes mellitus ocular complications**:**

a) **Retinal detachment**. This is caused by the accumulation of fluid between the neural retina and the retinal pigment epithelium and in non-diabetes patients most commonly results from a tear in the retina (rhegmatogenous retinal detachment). In patients with proliferative diabetic retinopathy, tractional retinal detachment may occur due to condensation and contraction of the vitreous gel in association with hemorrhage and fibrosis (plus gliosis). Tractional retinal detachment may progress to combined tractional and rhegmatogenous retinal detachment. Central vision is lost when the macula is involved.

b) **Rubeosisiridis and rubeotic glaucoma**. Rubeosisiridis is the growth of new vessels on the iris in eyes with advanced retinal ischaemia. Rubeosis – neovascularization of iris may induce a severe form of intractable glaucoma with growth of new vessels in the anterior chamber angle. If uncontrolled, neovascularization leads to closure of the aqueous fluid drainage route in the anterior chamber angle of the eye by fibro-vascular tissue.

c) **Catarac**t refers to opacification of the lens and is common in older age populations. Age-related cataract occurs earlier in patients with diabetes(Wea, 2004).

d) **Diabetic retinopathy**. This is a chronic progressive, potentially sight-threatening disease of the retinal microvasculature associated with the prolonged hyperglycemia and other conditions linked to diabetes mellitus such as hypertension.

Pathogenesis of diabetic retinopathy

Diabetes damages retinal capillaries through prolonged exposure to hyperglycemia. This leads to loss of supporting pericyte cells and tight junctions between the endothelial cells resulting in retinal edema, capillary closure and ischemia. An ischemic retina produces vascular endothelial growth factor which stimulates new vessel growth. An edematous or ischemic retina loses function and this reduces vision of the central retina or macular. New vessels are prone to bleeding (vitreous hemorrhage) and the accompanying fibrosis leads to tractional retinal detachment. Thus the sight threatening manifestations of diabetic retinopathy are proliferative retinopathy and diabetic maculopathy.

Non-proliferative retinopathy is the less serious form and occurs when an abnormality develops in the retinal capillaries, allowing fluid to leak into the tissue of the eye. The most common signs include hemorrhages, cotton wool spots, dilated retinal veins, and hard exudates. Many patients with non-proliferative retinopathy may not notice a change in their vision. Vision may be reduced if blood, lipids, or exudates start to leak into the retina near the macula or if ischemia occurs. The macula may begin to thicken and cause macular edema.

As time passes, non-proliferative retinopathy may progress into proliferative retinopathy due to increasing ischemia. Lack of oxygen to the eye may cause neovascularization around the optic disc, iris, or across the retina. The patient still may not have noticed a

direct opthalmoscope and also how to use the slit lamp. During this training, the researcher had the opportunity to examine the retina of normal eyes. This lasted for two

months (December 2014 to January 2015). In the month of February 2015, the researcher still under ophthalmologist guidance was shown the different eye features of diabetic retinopathy to look for during fundoscopy/slit lamp examination. Data collection commenced in March 2015.

A comprehensive ocular examination was performed on all study subjects by the researcher and confirmed by a trained ophthalmologist. The patients' eyes were examined in the following order: Visual acuity recorded using Snellen's chart (the presenting and best corrected visual acuity was documented separately for each eye). Anterior segment was then examined using a slit lamp and an ophthalmoscope. The fundus findings were graded using the International clinical diabetic retinopathy disease severity scale (see appendix 7 for details).If both eyes had features of diabetic retinopathy, the findings in the worse eye were used for grading.

CHAPTER THREE: RESEARCH QUESTIONS, JUSTIFICATION AND OBJECTIVES.

3.1 Research problem

Kenya is one of the 6 African countries with high prevalence of diabetes and in 2014 about1.7 million kenyans had diabetes mellitus. One of the micro-vascular complications of diabetes is diabetic retinopathy. Diabetic retinopathy is expected to increase in tandem with the increase in number of cases of diabetes mellitus because of poverty and other factors which prevent many kenyans from seeking the optimal treatment of the disease hence they develop risk factors associated with the development of diabetic retinopathy. Therefore, many people will develop preventable blindness due to diabetic retinopathy hence negatively affecting the work force of the nation. Also with poor sight, the patients will not actively participate in the management of their own health. This study aims to bring out the number of cases of diabetic retinopathy in Moi Teaching and Referral hospital and highlight the contributory risk factors. This will form the platform on which the hospital can come up with measures to prevent the avoidable blindness among its patients.

3.2 Justification

Many cross sectional studies have been done on the prevalence as well as the associated risk factors for developing diabetes retinopathy in other parts of the world as well as Kenya. Moi Teaching and Referral Hospital does not have data on the prevalence of diabetic retinopathy and the particular risk factors contributing to the condition hence this research work aims at addressing this gap. The expected increase in prevalence of diabetes will affect mostly the type 2 diabetes mellitus hence the choice of this study population. In addition, diabetic retinopathy is one of the targeted nine causes of global blindness in VISION 2020. Therefore, accurate identification of risk factors responsible for diabetic retinopathy is essential if effective preventative measures are to be developed. It is hoped

that by publishing of such data at the hospital, it level will stimulate interest in development of programs aimed at prevention through early diagnosis, management of risk factors and treatment of advanced cases.

3.3 Research questions

What is the prevalence rate of diabetic retinopathy among patients with type 2 diabetes mellitus at Moi Teaching and Referral Hospital?

What are the risk factors for developing diabetic retinopathy among the patients with type 2 diabetes mellitus?

3.4 Broad objective

To determine the prevalence and grades of diabetic retinopathy in patients with type 2 diabetes mellitus and the associated risk factors.

3.5 Specific objectives

1.To determine the prevalence of diabetic retinopathy in patients with type 2 diabetes mellitus

2.To determine the grades of diabetic retinopathy in patients with type 2 diabetes mellitus

3.To describe the association between risk factors and diabetic retinopathy in patients with type 2 diabetes mellitus.

CHAPTER FOUR: METHODOLOGY

4.1 Research design

The study design was cross-sectional.

4.2 Study area and Population

This study was conducted at Moi Teaching and Referral Hospital which is a referral Hospital for Western Kenya and Rift valley. The participants are patients with type 2 diabetes mellitus recruited from the diabetes clinic and in-patient adult wards.

4.3 Sampling technique.

This study employed simple random sampling technique. There are approximately 3000 patients with diabetes mellitus on follow up in diabetes clinic in Moi Teaching and Referral Hospital. About 30 to 70 patients are attended to during the clinic days. Patients were recruited during the clinic day (Tuesday, Thursday and Friday). The attendance list which had names of patients booked on a particular clinic day was used as a sampling frame. The participants were then randomly selected from the attendance list using a sampling table. Any patient who failed to turn up for the clinic or did not meet the inclusion criteria was replaced by randomly picking another from the list. An average of five patients were picked in a clinic day. The patients in the wards were enrolled on Monday and Wednesday. The admission list of the patients in the wards was used as the sampling frame. A sampling table was used to randomly select the participants. Any participant who failed to meet the inclusion criteria was replaced by another from the admission list by random selection. Any in-patient who had participated in a previous sampling was not included in subsequent ones.

4.4 Sample size

The sample size calculated was 325 respondents derived using the Fishers formula (shown below) ata prevalence of 30.4% derived from a previous study done by H.E. Nkumbe, K. H. M. kollmann and H.C. gaeckle on assessment of diabetic retinopathy in black kenyan type 2 diabetics in Kenyatta National Hospital and published in, *East African medical journal vol. 87 no. 3 March 2010*

$$\mathbf{n} = \frac{Z^2\ \hat{p}(1-\hat{p})}{\mathbf{e}^2}$$

Where:

n=sample size; z=level of confidence (95%); p=prevalence (30.4%); e=acceptable sampling error (5%)

4.5 Eligibility criteria

(a) Inclusion criteria

- Available documentary evidence (medical chart/file) of diagnosis of type 2 diabetes mellitus.

(b) Exclusion criteria

- Ocular diseases precluding slit lamp examination/ophthalmoscopy.
- Inability of a participant to consent

4.6 Participant screening, enrollment and treatment

Clients with type 2 diabetes mellitus on follow up in the diabetes clinic and those admitted in the adult wards were randomly approached by the researcher/research assistant and after

consenting, were recruited into the study upon meeting all the inclusion criteria. The researcher/research assistant took the patient's bio data and a comprehensive medical history of current and past illnesses, including duration of diabetes, history of hypertension, and medication use (anti-diabetes, anti-hypertensive and lipid lowering agents). The researcher/research assistant then took anthropometric measurements i.e. weight (kilograms) and height (meters) of the participant using standardized techniques. The body mass indexwas calculated using the formula (weight / height). Blood pressure was recorded in the sitting position in the right arm using a mercury sphygmomanometer (see appendix 3). Blood samples for glycated hemoglobin were obtained by finger prick from all patients by the researcher/research assistant (see appendix 4).Blood samples for lipid profile were drawn by the researcher/research assistant from patients who had fasted for >8 hours. Any participant who had not fasted for the time period was given a re-appointment(see appendix 6). The procedure for drawing blood is explained in appendix 5. All laboratory investigations were carried out at the AAR Eldoretlaboratory according to good laboratory and clinical practices. The participant were then be escorted by the researcher/research assistant to the eye clinic. In the eye clinic, the researcher determined the visual acuity of the participant using Snellens chart and then instilled 1-2 drops of 1% tropicaimide in each eye. Duration of 10 to 15 minutes was given for pupil dilatation before examination under a slit lamp and direct opthalmoscope respectively for features of diabetic retinopathy and diabetic macula edema. The findings were confirmed by a trained ophthalmologist before grading the participant degree of diabetic retinopathy using the International clinical diabetic retinopathy disease severity scale (see appendix 7).

The findings (body mass index, lipid panel, glycated hemoglobin and eye examination) were communicatedto the participant. Any participant with abnormalities in these findings

were referred accordingly (both internally and externally) to various teams including nutritionists, physicians and ophthalmologists. The researcher also started an intervention that might help ameliorate any abnormal findings.

4.7 Duration of type 2 diabetic retinopathy

Respondents were assigned into 3 groups based on the number of years they had had the disease since diagnosis. These groups were below 5 years, 5 to 10 years and over 10 years.

4.8 Eye examination

Prior to the start of data collection, the researcher under the guidance of a trained ophthalmologist was taken through the technique of doing fundoscopy using a hand held direct opthalmoscope and also how to use the slit lamp. During this training, the researcher had the opportunity to examine the retina of normal eyes. This lasted for two months (December 2014 to January 2015). In the month of February 2015, the researcher still under ophthalmologist guidance was shown the different eye features of diabetic retinopathy to look for during fundoscopy/slit lamp examination. Data collection commenced in March 2015.

A comprehensive ocular examination was performed on all study subjects by the researcher and confirmed by a trained ophthalmologist. The patients' eyes were examined in the following order: Visual acuity recorded using Snellen's chart (the presenting and best corrected visual acuity was documented separately for each eye). Anterior segment was then examined using a slit lamp and an ophthalmoscope. The fundus findings were graded using the International clinical diabetic retinopathy disease severity scale (see appendix 7 for details).If both eyes had features of diabetic retinopathy, the findings in the worse eye were used for grading.

4.9 Data analysis

Validation of the data was done before it was entered into the computer for analysis using SPSS. Descriptive statistics are presented using frequency table and cross tabulations while continuous variables with means, medians and standard deviation. Univariate and multivariate generalized linear models was used to assess associations of clinical, biochemical and anthropometric variables with diabetic retinopathy. The associations are presented in form of odds ratio and 95% confidence intervals. The univariate analyses that showed significant relationships ($p < 0.05$) between exposure variables and diabetic retinopathy were included into the multivariate analysis.

4.10Study limitations

1. The performance of examinations through a dilated pupil by direct ophthalmoscopy is 50-70% that of the gold standards meaning some early cases of diabetic retinopathy could have being missed.

4.11 Ethical considerations.

Ethical clearance was obtained from the Institutional Research and Ethics Committee (IREC) of Moi Teaching and Referral Hospital (MTRH) and Moi University School of Medicine and permission from MoiReferral and Teaching Hospital management.

A written informed consent was obtained from all the participants. Confidentiality was maintained when recruiting and handling data. Arising medical information was used and shared in patient treatment.

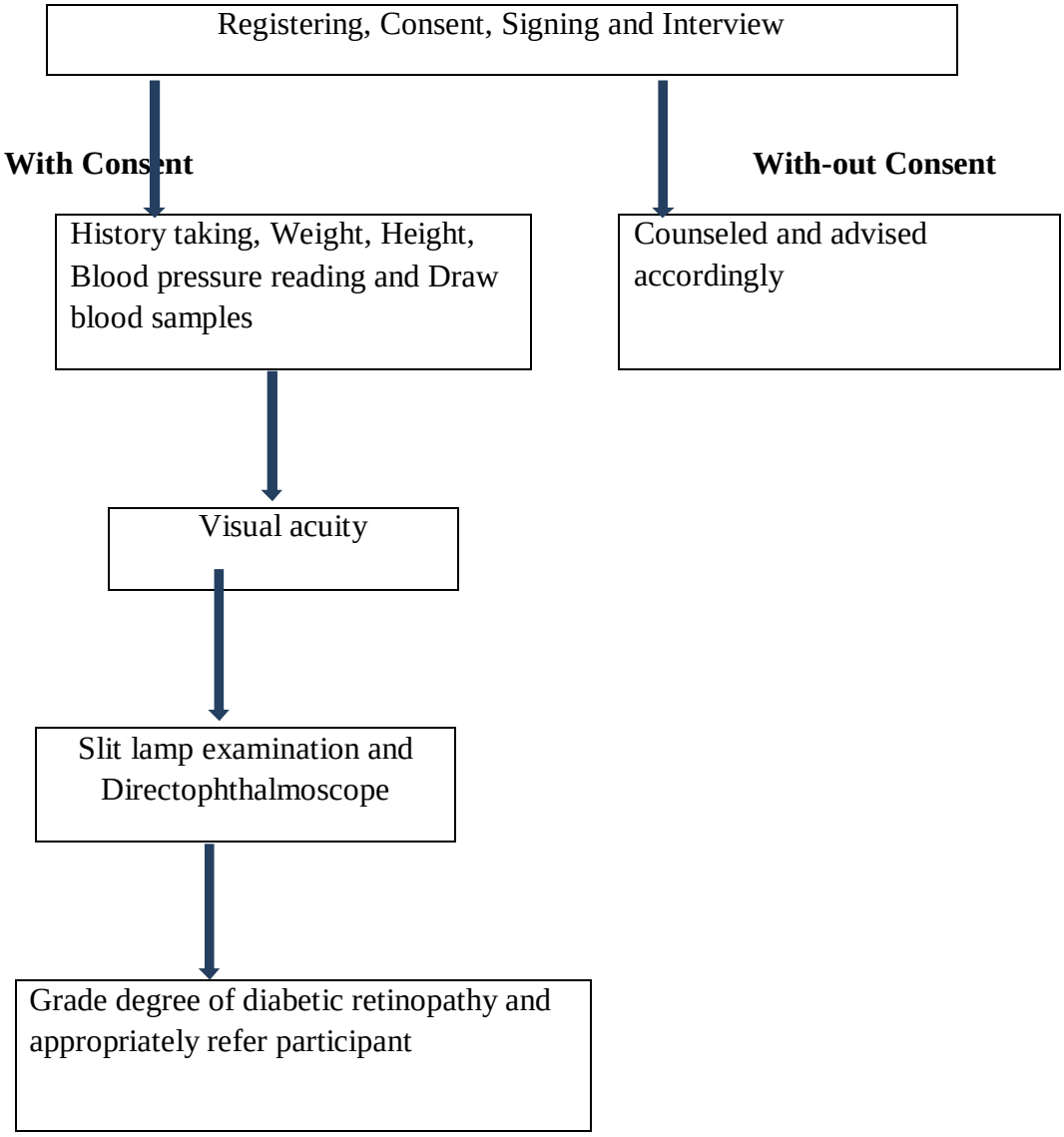

Figure 3: Diagram of patients flow during study

CHAPTER FIVE: RESULTS

A total of 413 participants were enumerated for this study. Of these, 329 participants consented and underwent examination to give a response rate of 79.7%. Eighty-four participants were excluded as shown in figure 4.

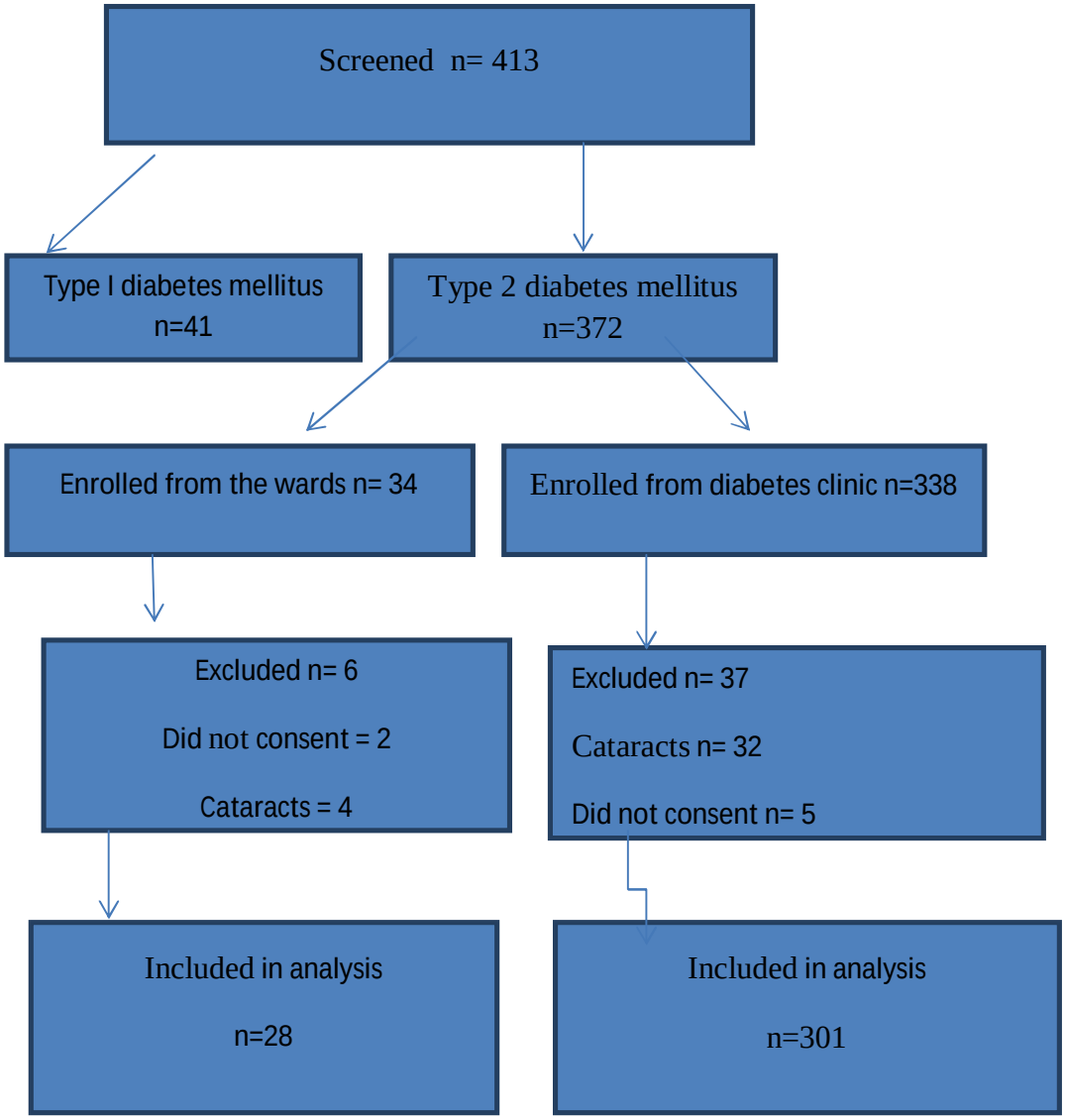

Figure 4: Study flow algorithm

Among the 329 participants included in the final analysis,187 (57%) were female (figure 5) with the mean age 56.8 years (SD 10.97).

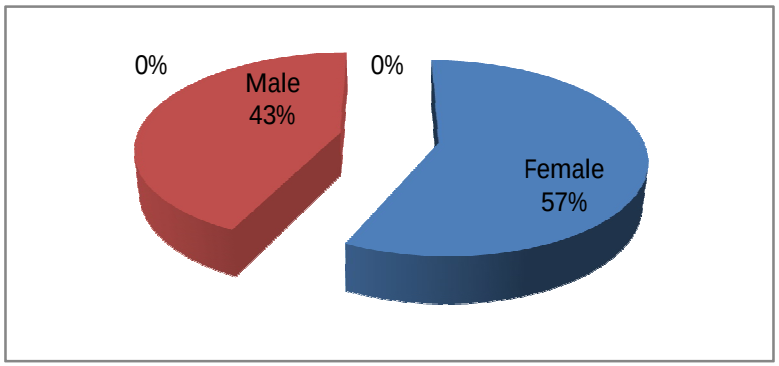

Figure 5: Pie chart showing distribution of gender

The mean body mass index was 27(SD 5). An estimated 184 (56%) of participants reported being hypertensive with the median blood pressure being 133/80 mmHg (IQR 120/70-150/89). The median duration of diabetes mellitus was 5 years (IQR 2-11) with a median glycated hemoglobinand total cholesterol of 8.65% (IQR7.2-11) and 4.48 mmol/l (IQR 3.59-5.37) respectively. Other clinical and laboratory parameters are summarized in Table 4 and 5 respectively below.

Table 4: Overall clinical characteristics

Variable	N	Mean (SD); median(IQR); proportion%
Age (years)	329	56.8 (10.99)
Weight (kg)	326	72(64-84)
Body mass index	326	27(5)
Blood pressure (mmHg)	329	133/80(120/70-150/89)
Duration of diabetes (years)	329	5 (2-11)
Hypertension	329	
Yes	184	56%
No	145	44%
Eye symptoms	293	
Yes	74	22%
No	255	78%
Previous checkup	329	
Yes	73	22%
No	256	78%

Table 5: Laboratory parameters

Variable	N	Median(IQR)
HbA1c (%)	329	8.65 (7.2-11)
Total cholesterol (mmol/l)	329	4.5(3.59-5.44)
HDL-c (mmol/l)	329	1.03(0.84-1.29)
LDL-c (mmol/l)	293	2.97(2.34-3.78)
Triglycerides (mmol/l)	329	1.73(1.15-2.51)

An estimated 51% of the participants were on insulin, 63% on oral hypoglycemic agents with an estimated 17% receiving both insulin and oral hypoglycemic agents. Among the 184 hypertensive patients, the most common antihypertensive drugs in use was enalapril

86(47%), calcium channel blockers 87 (47%), hydrochlorothiazide 76(41%) and losartan 47(26%). A total of 31 patients (9.4%) of all the participants were on atorvastatin.

The prevalence of diabetic retinopathy was 31% (95%CI 26-37%). Among patients with diabetic retinopathy,79 (81%) had mild to moderate non-proliferative diabetic retinopathy with the remainder having either severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy in nearly equal proportions. An estimated 12% (39) of participants had macula edema. Table 6summarizes the prevalence and distribution of diabetic retinopathy

Table 6: Prevalence and class of diabetic retinopathy and macula edema

Variable	**N**	**proportion%**
Diabetic retinopathy	329	
Yes	103	31%
No	226	69%
Diabetic retinopathy class	329	
1 No apparent diabetic retinopathy	228	69%
2 Mild non-proliferative diabetic retinopathy	36	11%
3 Moderatenon-proliferative diabetic retinopathy	43	14%
4 Severe non-proliferative diabetic retinopathy	10	3%
5 Proliferativediabeticretinopathy	9	2%
Macula edema	329	
Yes	39	12%
No	290	88%

When we compared clinical and laboratory characteristics between patients with and without diabetic retinopathy, there were statistically significant differences between some of the risk factors identified a priori. For Instance, patients with diabetic retinopathy were older, mean age 59.6 years versus 55.9 years (p-0.008), compared to those without. As illustrated in Table 7**,** patients with diabetic retinopathy had a higher prevalence of hypertension, a higher mean systolic blood pressure, a longer duration of diabetes, higher glycated hemoglobin and higher total cholesterol and low density lipoprotein concentration.

Table 7: Comparison of clinical and laboratory characteristics by diabetic retinopathy status

Variable	Diabetic retinopathy present (mean,sd; n, %)	No diabetic retinopathy	P-Value
Age (years) (mean; Sd)	59.6 (9)	55.9(11)	**0.008**
Gender n (proportion %) Male Female	 46 (45%) 57 (55%)	 88 (44%) 113 (56%)	 0.60
BMI	27.0 (4.5)	27.2 (5.4)	0.78
Blood pressure (mmHg) **Systolic** **Diastolic**	 143 (23) 81.4 (14.2)	 131 (22.1) 78.8 (12.7)	 **0.0001** 0.06
Duration of diabetes (years)	10.3 (7.3)	6.3 (6.7)	**0.0001**
Hypertension **Yes** **No**	 72(70%) 31(30%)	 112 (50%) 114 (50%)	 **0.002**
Glycated hemoglobin (%)	10.3 (2.3)	8.7 (2.3)	**0.0001**
Total cholesterol (mmol/l)	4.9 (1.2)	4.44 (1.3)	**0.0001**
HDL-c (mmol/l)	1.06 (0.34)	1.09 (0.37)	0.51
LDL-c (mmol/l)	3.6 (1)	2.8 (1)	**0.0001**
Triglycerides (mmol/l)	2.0 (0.87)	2.01(1.4)	0.88
Eye symptoms **Yes** **No**	 31(34%) 61 (66%)	 32(16%) 190(84%)	
Previous checkup **Yes** **No**	 35(34%) 68(66%)	 38(17%) 188(84%)	

35% (114) of the participants were aged between 51 to 60 years while 158 (48%) had the glycated hemoglobin range between 7-10% and 147 (45%) of participants had had diabetes for less than five years.

Table 8 below summarizes the other clinical and laboratory parameters patients in the various risk categories for diabetic retinopathy.

Table 8: Distribution of clinical and laboratory parameters in pre-specified categories among those with and without diabetic retinopathy

	Overall		**With diabetic retinopathy**		**Without diabetic retinopathy**	
Variable	**N**	**Proportion %**	**n**	**Proportion %**	**N**	**Proportion%**
Age group (years)	329		103		226	
0= <30	0	0%	0	0%	0	0%
1=30 to 40	27	8%	3	3%	24	11%
2= 41 to 50	60	18%	11	11%	49	22%
3= 51 to 60	114	35%	44	43%	70	31%
4= 61 to 70	97	29%	34	33%	63	28%
5= >70	31	10%	11	10%	20	9%
Duration of diabetes (years)	329		103		226	
1= <5	147	45%	31	30%	116	51%
2= 5 to 10	78	23%	24	23%	54	24%
3= >10	104	32%	48	47%	56	25%
Body mass index category	329		103		226	
1= Underweight <18.5	7	2%	1	1%	6	3%
2= Normal 18.5 – 24.9	107	33%	33	32%	74	33%
3= Overweight 25-29.9	126	38%	42	41%	84	37%
4= Obese >30	89	27%	27	26%	62	27%
Glycated hemoglobincategory (%)	328		103		225	
1= <7	60	18%	4	4%	56	25%
2= 7 – 10	158	48%	47	46%	111	49%
3= >10	110	34%	52	50%	58	26%
Systolic blood pressure category (mmHg)	329		103		226	
Normal: <140	193	59%	43	42%	150	66%
Stage 1:140-159	87	26%	34	33%	53	23%
Stage 2:160-179	35	11%	20	19%	15	7%
Stage 3: ≥ 180	14	4%	6	6%	8	4%
Diastolic blood pressure category(mmHg)	329		103		226	

Normal <90	247	75%	68	66%	179	79%
Stage 1: 90 to 99	56	17%	21	20%	35	16%
Stage 2: 100 to 109	17	5%	10	10%	7	3%
Stage 3: ≥ 110	9	3%	4	4%	5	2%
Total cholesterol category (mmol/l)	329		103		226	
Normal <5.2	231	70%	60	58%	171	76%
Borderline 5.2 – 6.2	59	18%	23	22%	36	16%
High >6.2	39	12%	20	20%	19	8%
Low density lipoprotein category (mmol/l)	329		103		226	
Normal <3.3	189	57%	36	35%	153	68%
Borderline 3.4 – 4.1	74	23%	27	26%	47	21%
High >4.1	66	20%	40	39%	26	11%
Visual acuity right	317		98		219	
Normal :6/6 to 6/18	214	68%	50	51%	164	75%
Impaired: <6/18 to 6/60	74	23%	32	33%	42	19%
Severe: <6/60 to 3/60	8	2%	4	4%	4	2%
Blind <3/60	21	7%	12	12%	9	4%
Visual acuity left	315		96		219	
Normal :6/6 to 6/18	209	66%	52	54%	157	72%
Impaired: <6/18 to 6/60	66	21%	28	29%	38	17%
Severe: <6/60 to 3/60	17	6%	7	7%	10	5%
Blind <3/60	23	7%	9	10%	14	6%

In the univariate model of risk factors associated with diabetic retinopathy (ungrouped data), every increase in age by a year (OR1.08(95% CI 1.03-1.11; p 0.0001); presence of hypertension (OR 2.36(95% CI 1.44-3.87; p 0.001) or elevated systolic blood pressure (OR 1.02 95% CI 1.01-1.03; p 0.0001) were associated with diabetic retinopathy. Other risk factors that were statistically significant in this model include every point increase in glycated hemoglobin, total cholesterol and low density lipoprotein levels. These results are illustrated in Table 9a.

Table 9a: Univariate analysis of risk factors associated with diabetic retinopathy (ungrouped)

Variable	Odds ratio (95%CI)	P-Value
Age	1.03 (1.01-1.06)	**0.009**
Gender **Male** **Female**	 1.13 (0.71-1.81) 1	 0.602
Duration of diabetes	1.08(1.03-1.11)	**0.0001**
Hypertension **Yes** **No**	 2.36(1.44-3.87) 1	 **0.001**
Weight	0.99(0.98-1.01)	0.64
Body mass index	0.99(0.96-1.04)	0.78
Glycated hemoglobin	1.31 (1.18-1.45)	**0.0001**
Systolic blood pressure	1.02(1.01-1.03)	**0.0001**
Diastolic blood pressure	1.01(0.99-1.03)	0.11
Total cholesterol	1.59(1.28-1.97)	**0.0001**
High density lipoprotein	0.81(0.42-1.54)	0.517
Low density lipoprotein	2.28 (1.7-3.0)	**0.0001**
Triglycerides	1.01(0.84-1.22)	0.87

In the adjusted multivariate model (ungrouped data), longer duration of diabetes (OR 1.06; 95%CI 1.02-1.10; p 0.003); higher glycated hemoglobin (OR 1.33; 95%CI 1.18-1.50; p 0.0001); higher systolic blood pressure (OR 1.02; 95% CI 1.01-1.03; p 0.011) and higher low density lipoprotein (OR 2.10; 95%CI 1.51-2.92; p 0.0001) were independently associated with diabetes retinopathy. These results are illustrated in Table 9b

Table 9b: Multivariate logistic regression of factors associated with diabetic retinopathy (ungrouped)

```
. logistic dmretinopathy durationdm htn hba1c bps tc ldl

Logistic regression                                     Number of obs   =        328
                                                        LR chi2(6)      =      86.96
                                                        Prob > chi2     =     0.0000
Log likelihood = -160.62939                             Pseudo R2       =     0.2130

------------------------------------------------------------------------------
dmretinopathy | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
   durationdm |   1.061275   .0213093     2.96   0.003      1.02032    1.103873
          htn |   1.394532   .4582757     1.01   0.312     .7323247    2.655542
        hba1c |   1.333672   .0806806     4.76   0.000     1.184556    1.501559
          bps |   1.017795    .007018     2.56   0.011     1.004133    1.031643
           tc |   .8858415   .1122654    -0.96   0.339     .6910041    1.135616
          ldl |   2.103776   .3526821     4.44   0.000     1.514614    2.922113
        _cons |   .0002212   .0002687    -6.93   0.000     .0000205    .0023924
------------------------------------------------------------------------------
```

Variable	Odds ratio (95%CI)	P-Value
Duration of diabetes	1.06(1.02-1.10)	**0.003**
Hypertension	1.39(0.73-2.66)	0.312
Glycated hemoglobin	1.33(1.18-1.50	**0.0001**
Systolic blood pressure	1.02(1.00-1.03)	**0.011**
Total cholesterol	0.89(0.69-1.14)	0.339
Low density lipoprotein	2.10(1.51-2.92)	**0.0001**

When data was grouped into pre-specified risk categories for diabetic retinopathy (illustrated in Table 10),age group above 50 years compared to the 30-40 years age group was associated with increased risk for diabetic retinopathy. Other risk factors that had statistically significant association with diabetic retinopathy in the univariate model included: duration of diabetes >10 years compared to <5 years,glycated hemoglobin>7%,blood pressure >140/100 mmHg, elevated total cholesterol above 5.2 mmol/l and elevated low density lipoprotein>3.3mmol/l.

Table 10: Univariate analysis of risk factors associated with diabetic retinopathy (grouped data)

Variable	Odds ratio (95%CI)	P-Value
Age group (years)		
1=30 to 40	1*	
2= 41 to 50	2.14(0.42-10.8)	0.354
3= 51 to 60	7 (1.55-31.5)	**0.011**
4= 61 to 70	5.8(1.28-26.3)	**0.023**
5= >70	5.25(1.00-27.5)	**0.050**
Duration of diabetes (years)		
1=<5	1*	
2= 5 to 10	1.60(0.86-2.99)	0.136
3= >10	3.10(1.78-5.38)	**0.0001**
Glycated hemoglobin category (%)		
1= <7	1*	
2= 7 – 10	5.93(2.03-17.2)	**0.001**
3= >10	12.55(4.25-37.00)	**0.0001**
Systolic blood pressure category (mmHg)		
Normal: <140	1*	
Stage 1:140-159	2.23(1.29-3.87)	**0.004**
Stage 2:160-179	4.65(2.19-9.85)	**0.0001**
Stage 3: ≥ 180	2.61(0.86-7.95)	**0.09**
Diastolic blood pressure category (mmHg)		
Normal <90	1*	
Stage 1: 90 to 99	1.58(0.85-2.90)	0.141
Stage 2: 100 to 109	3.76(1.37-10.27)	**0.010**
Stage 3: ≥ 110	2.10(0.55-8.07)	0.277
Total cholesterol category (mmol/l)		
Normal <5.2	1*	
Borderline 5.2 – 6.2	1.82(0.99-3.32)	**0.05**
High >6.2	3.0(1.50-6.0)	**0.002**
Low density lipoprotein category (mmol/l)		
Normal <3.3	1*	
Borderline 3.4 – 4.1	2.46(1.35-4.46)	**0.003**
High >4.1	6.84(3.69-12.70)	**0.0001**

In the multivariate analysis using grouped data (table 11), age group 51-60 years compared to 30-40 years (OR 6.59; 95% CI 1.04-41.8; p 0.046); duration of diabetes above 10 years compared with <5 years (OR 3.50(95% CI 1.82-6.77; p 0.0001), glycated hemoglobin 7-10% or > 10% (OR 5.34(95% CI 1.63-17.48; p 0.006) and (OR 12.95(95% CI 3.82-43.84; p 0.000) respectively, systolic blood pressure 160-179 mmHg compared to <140mmHg (OR 4.94(95% CI 1.97-12.39; p 0.001) and low density lipoprotein >3.3mmol/l (OR 2.99(95% CI 1.45-6.16; p 0.003) were independently associated with diabetic retinopathy.

Table 11: Multivariate logistic regression of factors associated with diabetic retinopathy (grouped data).

Variable	**Odds ratio (95%CI)**	**P-Value**
Age group (years)		
1=30 to 40	1*	
2= 41 to 50	1.24(0.16-9.15)	0.829
3= 51 to 60	6.59(1.04-41.8)	**0.046**
4= 61 to 70	3.24(0.49-21.2)	0.219
5= >70	1.52(0.17-12.8)	0.702
Duration of diabetes (years)		
1= <5	1*	
2= 5 to 10	2.04(0.97-4.27)	0.058
3= >10	3.50(1.82-6.77)	**0.0001**
Glycated hemoglobin category (%)		
1= <7	1*	
2= 7 – 10	5.34(1.63-17.48)	**0.006**
3= >10	12.95(3.82-43.84)	**0.0001**
Systolic blood pressure category (mmHg)	1*	
Normal: <140	2.06(1.06-4.01)	**0.033**
Stage 1:140-159	4.94(1.97-12.39)	**0.001**
Stage 2:160-179	1.63(0.39-6.87)	0.505
Stage 3: ≥ 180		
Diastolic blood pressure category (mmHg)	1*	
Normal <90	1.27(0.59-2.69)	0.533
Stage 1: 90 to 99	1.82(0.53-6.14)	0.335

Stage 2: 100 to 109 Stage 3: ≥ 110	0.84(0.14-4.91)	0.848
Total cholesterol category (mmol/l) Normal <5.2 Borderline 5.2 – 6.2 High >6.2	 1* 0.71(0.32-1.54) 0.56(0.22-1.44)	 0.383 0.231
Low density lipoprotein category (mmol/l) Normal <3.3 Borderline 3.4 – 4.1 High >4.1	 1* 2.99(1.45-6.16) 6.72(3.04-14.87)	 **0.003** **0.0001**

* Reference category

Table 12: Cross tabulation of diabetic retinopathy and macula edema

Diabetic retinopathy	**Macula edema**		
	Absent	**Present**	**Total**
Absent	225	1	226
Present	65	38	103
Total	290	39	329

Among the 39 patients with macula edema, 38 (97%) had concomitant diabetic retinopathy. Among 103 patients with diabetic retinopathy 38 (36.9%) had concomitant macula edema.

Table 13: Cross tabulation of eye symptoms and having a previous check up

Eye symptoms	**Previous checkup**		
	No	**Yes**	**Total**
Absent	215	40	255
Present	41	33	74
Total	256	73	329

Among 73 patients who reported having eye symptoms, 40 (54.8%) had had a previous eye checkup. Yet among 255 patients without eye symptoms only 40 (15.7%) reported having had previous eye checkup.

CHAPTER SIX: DISCUSSION

Diabetic retinopathy is becoming a major cause of blindness throughout the world in the age group of 20 to 60 years (Global initiative for the elimination of avoidable blindness, 1997).Loss of productivity and quality of life for the patient with diabetic retinopathy will lead to additional socio-economic burdens on the community. In this study the overall prevalence of diabetic retinopathy was 31%.This prevalence rate is closely aligned with previous studies done in Africa and Kenya. Mbanya JC, Sobngwi E, (2003)looked at data for the prevalence of diabetic complications in Africa and reported that retinopathy was present in 16–55% of people with diabetes. Kohner, Stratton, et al (1998) did a large systematic review of the epidemiology of diabetic retinopathy and maculopathy in Africa identified 62 studies from 21 countries, including 3 surveys, 2 cohort studies, 5 case-control studies and 52 clinic-based studiesand among the three population-based studies from Nigeria, Egypt and Mauritius, the reported prevalence of diabetic retinopathy among patients with type 2 diabetes ranged from 30.2– 31.6%. Similar studies done in Kenya in Nakuru (Mathenge et al., 2014)and Embu(Njambi et al., 2012)reported a prevalence rate of 35.9% and 41% respectively and almost 50 per cent of diabetics at Kenyatta National Hospital(Kariuki, Kollmann et al., 1999).

The estimated prevalence of macula edema is 12% which is way above 4.7% reported by Njambi (2012) in but less than 33.3% as found byMathenge(2014) in Nakuru. This might be because the study in Nakuru incorporated color fundus photography in diagnosing diabetic retinopathy and macula edema which is more sensitive than slit lamp examination orophthalmoscopy. Generally, the prevalence of diabetic macula edema among patients

with diabetes is generally much lower than that of diabetic retinopathy (Bertelsen et al., 2013).Among the population-based studies, prevalence of diabetic macula edema among patients with type 2 diabetes was between 1.4 and 12.8 %(Roy, Klein et al., 2004)

Cataracts was a major reason for exclusion because the condition is very frequent in diabetes as evidenced by Rotimi et al (2003) in a cohort study that showed cataracts to be a more important cause of visual impairment than diabetic retinopathy in patients with diabetes.

Gender did not attain a statistical significance as a risk factor for diabetic retinopathy. This is in contrast to other studies which have shown varying results when predicting sex as a risk factor for developing diabetic retinopathy. Male preponderance in diabetic retinopathy has been shown in India(Rema, Premkumar, et al., 2005), United Kingdom Prospective Diabetes Study Group, (1998)and a study of Pima Indians(Nagi, Bennett, et al.,1997).Body mass index was not a risk factor for development of diabetic retinopathy.Theevidence supporting a relationship between high body mass index and increased risk of diabetic retinopathy is inconclusive (Turner, 1998).Some studies have demonstrated a relationship between obesity or higher body mass index andanincreased riskof diabetic retinopathy(Kohner, Stratton, et al, 1998), whereas others have reported conflicting results (Klein R, Klein B, et al., (1992).

Increasing age was positively associated with increasing risk of diabetic retinopathy. In the multivariate analysis using grouped data, age group 51-60 yearsandevery increase in age by a yearwas independently associated with increased risk of diabetic retinopathy. This apparent association between older age and diabetic retinopathy might be due to colinearity between old age and longer duration of diabetes. Furthermore, it is believed that undiagnosed type 2 diabetes mellitus may occur 4 – 12 years before its clinical

diagnosis and that diabetes may be present for five years before the onset of retinopathy (Ramachandran, Snehalatha et al., 1996), (Harris, Welborn et al 1992) thus the preponderance of diabetic retinopathy in old age.

Duration of diabetes above 10 years, glycated hemoglobin > 10%, systolic blood pressure 160-179 mmHg and low density lipoprotein >3.4mmol/l were independently associated with diabetic retinopathy. The duration of diabetes has consistently been shown to be one of the most important determinants of diabetic retinopathy. It has been suggested that the duration reflects total glycemic control, a risk factor that involves cumulative damage(Dowse, Collins. et al., 1998). In this study, 104(32%) of the participants had duration ofdiabetes being more than ten years of whom (48)47% had some form of diabetic retinopathy. This is in contrast to the 147(45%) participants who had duration of diabetes beingless than five years and only 31(30%) had diabetic retinopathy.

High glycated hemoglobin was associated with diabetic retinopathy. Most of the participants, 158(48%), hadglycated hemoglobin between 7-10%. Only 47(46%) had some degree of diabetic retinopathy. This is in comparison to the 110(34%) participants who had glycated hemoglobin above 10% of whom 52(50%) had developed diabetic retinopathy. Only 4% of the participants with glycated hemoglobin below 7% had diabetic retinopathy.This findings compares with the United Kingdom Prospective Diabetes Study Group (1998) and the Diabetes Control and Complications Trials (1993) which provided strong evidence that tight control of glycemia(glycated hemoglobin<7 %) reduces the risk of development and progression of diabetic retinopathy in both type 1 and type 2 diabetes. The Diabetes Control and Complications Trials showed that intensive glycemic control reduced the incidence of retinopathy by 76 % and progression from early to advanced retinopathy by 54%**.** In Wisconsin Epidemiologic Study of

Diabetic Retinopathy (1991) the 10 year incidence of development of any grade of retinopathy increased 30% and 60% for each absolute 1% higher baseline glycated hemoglobin.

Most of the patients, 184 (56%), had hypertension as a co-morbidity. Systolic blood pressure above 160-179 mmHg was an independent risk factor for diabetic retinopathy following multivariate logistic regression of the data.Hypertension is recognized as a risk factor for the development and progression of diabetic retinopathy(Burgess, MacCormick, et al., 2013), (Chang, Chen, et al., 1990). Multiple epidemiologic studies have identified hypertension as a risk factor for diabetic retinopathy and diabetic macula edema (Kohner, Stratton, et al, 1998). In theUnited Kingdom Prospective Diabetes Study Group, (1998), tight blood pressure control (defined as target blood pressure <150/85 mmHg) in patients with type 2 diabetes reduced the risk of microvascular disease by 37 %, the rate of progression of diabetic retinopathy by 34 %, and the risk of deterioration of visual acuity by 47 %.

Univariate analysis of the lipid profile data showed total cholesterol and low density lipoproteins as risk factors associated with diabetic retinopathyand on multivariate logistic model, low density lipoproteinabove 3.4mmol/l was independently associated with increased risk of diabetic retinopathy. 231 (70%) had normal total cholesterol levels while 189(57%) had normal low density lipoproteins. The rest of the respondents had dyslipidemia. This is in contrast to previous studies which have found inconsistent results to link dyslipidemia as a risk factor for diabetic retinopathy.As outlined in a previous review, no single lipid measure had been consistently found to be associated with diabetic retinopathy or diabetic macule edema(Ding, Wong, 2012).In recent cohort studies, only

the Madrid Diabetes Study (2013) found an association between low density lipoproteincholesterol and incidence of diabetic

Among the 39 patients with macula edema, 38 (97%) had concomitant diabetic retinopathy while among 103 patients with diabetic retinopathy, 38 (37%) had concomitant macula edema. This is because diabetic retinopathy and diabetic macula edema have common risk factors as evidenced by a review conducted in 2012 which suggested that up to 7 % of people with diabetes may have diabetic macula edema and risk factors of diabetic macula edema are largely similar to diabetic retinopathy(Ding, Wong, 2012)

The number of participants who had visual acuity analyzed is way below the other parameters (277 instead of 293) because some of the patients were in-patients with reduced levels of consciousness hence could not cooperate. Among those analyzed, 32% of the participants had impaired/low vision which cannot be solely attributed to diabetic retinopathy. Despite the high percent of low vision, regular eye check up by an ophthalmologist is quite low as evidenced in this study where 73 (22.1%) patients had undergone a previous eye checkup. Yet among 230 patients without eye symptoms only 34 (15%) reported having had previous eye check-up. The most common eye symptom given was poor/hazy vision. Njambi et al (2012)in his study found that seventy one percent of the patients had never had an eye examination before by an ophthalmologist.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATIONS

7.1 Conclusions

Diabetic retinopathy is a major threat to the sight of patients with type 2 diabetes mellitus in Moi Teaching and Referral Hospital. Glycated hemoglobin >10%, duration of diabetes>10 years, low density lipoprotein >3.4 mmol/l and systolic hypertension were independently associated with increased risk of diabetic retinopathy.

7.2Recommendations

1. Restructuring of the existing diabetic eye screening programme to enhance prevention through early diagnosis.
2. The health workers managing patients with diabetes to intensify efforts aimed at controlling dyslipidemia, hypertension and high glycated hemoglobin.

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Appendices

Appendix One: Questionnaire

Prevalence of diabetic retinopathy and associated risk factors in type 2 diabetes

Name: ……. **Age**: … **Sex**: Male Female

Duration of diabetes mellitus……. **Hypertension:** Yes No

Medication: ……..

Weight (KG): …. **Height** (CM): ….. **BMI:** …...

HBA1c……..% **Blood Pressure** (mmHg)…….

Lipid profile (mg/dl): TC…… LDL…….

Any eye symptoms: ……

Have you had a previous eye check-up: Yes No

Visual acuity: R/E….. L/E …….

Is Diabetic Retinopathy present: Yes No

Is Diabetic Macula Edema Present: Yes No

Description of ophthalmoscopy findings

Left Eye	Right eye

Classification of DR:

- ❖ No apparent DR ☐
- ❖ Mild NPDR ☐
- ❖ Moderate NPDR ☐
- ❖ Severe NPDR ☐
- ❖ Proliferative diabetic retinopathy ☐

Comments on Treatment/Referrals/Follow-up:

……

Interviewer Signature……

Date:……

Appendix Two: Consent Form

A. ENGLISH

My name is Musawa Moses. I am a qualified doctor, registered by the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a master's degree in Internal Medicine at Moi University. I would like to recruit you into my research which involves looking into your eyes for possible complications related to diabetes mellitus.

About diabetic retinopathy

It is one of the complications of diabetes mellitus that leads to blindness. It is usually asymptomatic in its presentation and by the time you present with vision problems, the disease is very advanced. The only way to treat it is by prevention which involves ameliorating risk factors that makes it progress faster and also through screening of your eyes. If it is diagnosed earlier there is treatment for it. We will also get your blood samples to investigate some of the risk factors that put you at the danger of developing the complication

We will keep all your test results in confidence and keep you informed of the results. Treatment does not depend on your participation in this study. We will offer appropriate treatment for any condition that we find from assessing you and from your test results.

This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University/Moi Teaching and Referral Hospital.

If you need further clarifications please contact IREC using the address below.

The Chairman IREC,

Moi Teaching and Referral Hospital,

PO Box 3,

Eldoret.

Tel: 33471/2/3

My cell phone number is: 0711 640 910

Research Subject:

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed above. I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Signature of Subject …….

Name……

Date……..

B. KISWAHILI

Majinayangu ni Musawa Moses. Mimi nidaktarialiyefuzunakusajiliwanabodiyamadaktariya Kenya (Kenya Medical Practitioners and Dentists Board). Mimi nimsomiwashahadayajuu (Masters) yaudaktari (Internal medicine) katikachuokikuu cha Moi. Nafanyautafitikuhusukupofushwakwa macho kutokananaugonjwawakisukarinaningeombaushirikikatikahuuutafiti.

Upofu unaotokana na ugonjwa wa kisukari

Kupofushwa kwa macho nimojawapoyamadharayaugonjwawakisukari. Mgonjwamaramingihanadalilizozotezinazoonyeshakwambaugonjwahuuunadhuru macho zake.Dalilikamakupotezauwezowakuonainapotokezea, asilimiakubwayawagonjwahupofuka.Matibabumazuriyahiishidanikuzuiakwakufanyauchung uziwa macho kilamwakanapiakutibumagonjwamengineambayoinafanyaugonjwahuuwakupofushakueneak waharaka.

Damuitatolewakuchunguzakamakunamagonjwamengineinayofanyaupotezeuwezowakuonak waharaka.
Matokeoyakoyatawekwasalamabilakujulishayeyote.Tutakufahamishakuhusumatokeokwama nufaayaafyayako.
Tutakupamatibabuyafaayokulingananamagonjwayoyotetupatayowakatitunaendeleanauchun guzi.

Uwehurukuulizamaswaliyoyote.Uchunguzihuuumehidhinishwanakamatiyakusimamiautafiti (Institutional Research and Ethics Committee-IREC) katikachuokikuu cha MoinahospitaliyarufaayaMoi.

Iwapounahitajimaelezozaiditafadhaliwasilianana IREC kwakutumiaanwaniifuatayo.

Mwenyekiti IREC,

Moi Teaching and Referral Hospital,S. L. P. 3,

Eldoret.

Simu: 33471/2/3

Nambariyanguyasimuyarununu ni: 0711 640 910

HIDHINI YAKO:

Walio na miaka 18 na zaidi

Nimeelezwaipasavyoyakwambaninashirikikatikautafitiwausomiutakaochunguzaiwaponinauguaugonjwawakupofushwakwa macho unaosababishwa na viinivyaugonjwawakisukari.Mchunguzipiaamenielezakuwasitakosamatibabuyanguyakawaidaiwaponitashiriki au sitashiriki katik autafiti huu. Pia nimeelezwakuwasitahitajikakulipiachochotekinachohusiana na utafitihuu.

Sahihi: …….……Jina: ….……

Tarehe: ……

Appendix Three: Procedure for measuring blood pressure

Blood pressure will be taken using an Omron M2 compact upper arm blood pressure monitor (Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015).

The patient should be in a quiet place, in a relaxed sitting position with no tight fitting clothing on the upper arm, or any thick clothing such as a sweater.

The patient sits upright with the back straight and places the arm on the table so that the cuff is on the same level as the heart. The cuff is wrapped on the right arm such that the bottom of the cuff is at least 1cm above the elbow. It is then fastened snugly. The start button on the machine is then pressed and automatically the cuff begins to inflate and the machine takes a reading. The blood pressure results as well as a heart rate reading are then displayed on the screen.

Should an error occur, the cuff is deflated and the process is repeated. High blood pressure readings are confirmed manually using a mercury sphygmomanometer.

The blood pressure machines are calibrated every week.

Appendix Four: Procedure for glycated hemoglobin assays

HbA1c Analyzer used: Bayer DCA 2000®+Analyzer

Chemical Principles of procedure:

Both the concentration of haemoglobin A1C and concentration of total hemoglobin are measured and the ratio reported as percentage HbA1c. All of the reagents for performing both reactions are contained in DCA 2000® HbA1c reagent cartridge. For the measurement of total haemoglobin potassium ferricyanide is used to oxidize hemoglobin in the sample to methaemoglobin. The methemoglobin then complexes with thiocyanate to form thiocyanomethaemoglobin, the coloured species which is measured. The extent of color development at 53-nm is proportional to the concentration of total haemoglobin in the sample. For the measurement of specific HbA1c, an inhibition of latex agglutination assay is used. An agglutinator causes agglutination of latex coated with HbA1c specific mouse monoclonal antibody. This is measured as an increase in absorbance at 531nm.HbA1c competes for the limited number of antibody-latex binding sites causing an inhibition of agglutination and a decreased scattering of light. The decreased scattering is measured as a decreased in absorbance at 531nm.The HbA1c concentration is then quantified using a calibration curve of absorbance versus HbA1c concentration. All measurements and calculations are calculations are performed automatically by the DCA 2000+ Analyzer, and the screen displays percent HbA1c at the end of assay.

Procedure for HbA1c Assay; Procedure is explained to the subject and consent obtained. Subject's finger is swabbed with methylated spirit and allowed a few seconds to dry. The swabbed Finger pricked. A new plastic capillary holder is removed from a blister pack.

A drop of blood is placed at the end of glass capillary allowing the glass capillary to fill. A new reagent cartridge is opened up. The plastic capillary holder is placed into the reagent cartridge. The reagent cartridge holder is loaded into the DCA 2000® +Analyzer. Test results are automatically displayed in 6 minutes.

Calibration:

Instrument: The DCA 2000+Analyzer is calibrated by the manufacturer. Thereafter, the instrument automatically self-adjusts during first-time power up and during each assay. In the event of the system is unable to make appropriate internal adjustments, an error message is displayed.

Reagent:

The manufacturer calibrates the cartridges using parameters based on a DCCT reference method. The DCA 2000 HbA1c test method is National Glycohaemoglobin Standardization Program (NGSP) certified. The DCA 2000 HbA1c test method is traceable to International Federation of Clinical Chemistry (IFCC) reference materials and test methods. There is a calibration card for scanning for each lot of cartridges; the calibration bar code is read by the instrument. This assesses the appropriate calibration values for the particular lot. If no calibration curve is in use, the instrument prompts the user to scan the calibration card.

Quality Control:

To assure quality of both testing procedures and patient results for hemoglobin A1C, the DCA 2000+ system performs 48 optical, electronic, mechanical and reagent checks during the course of each specimen assay.

In addition to the above measures, each new lot had one kit used for assessing quality control by checking the HbA1c percent of healthy non diabetic persons.

Blood in plain Vacutainer® bottles are taken immediately to the lab. Serum may be stored for up to one day at 2 to 25oC, up to seven days at 4 to 8^{o}C and up to six months at -20 to -80^{o}C.

The bottle is set onto a centrifuge and spun at 3000 rpm for 3 minutes to separate the serum from the cells. The supernatant (serum) is carefully suctioned using a micropipette and transferred to a sample cup.

The sample cups are systematically set on a rack that goes onto a Cobas Integra® 400 plus analyzer (Roche Diagnostics, 9115 Hague Road, PO Box 50457, Indianapolis, IN 46250-0457). This is an autoanalyzer that uses the Jaffe reaction to quantify creatinine; creatinine reacts with picric acid in the presence of an alkaline pH to produce a yellow-red complex that has a maximum absorbance at 512nm. The rate of dye formation is proportional to the level of creatinine in the sample. The analyzer reads out this absorbance and based on its software it calculates the serum creatinine. It prints out the result on paper. The result is reported in µmol/L alongside reference serum creatinine levels.

Quality control checks are run daily.

Appendix Five: Procedure for drawing blood

The procedure is explained to the patient and verbal consent sought.

Universal precautions will be observed.

A tourniquet is applied at a distal site about 5cm proximal to the selected site of venipuncture. The patient makes a fist without pumping the hand. The phlebotomist puts on a pair of clean gloves. The selected site is cleaned thoroughly with methylated spirit or povidone Iodine starting with the center and working outward. It is then allowed to dry. The patient's arm is grasped firmly using the thumb to keep the skin taut and to anchor the vein. A sterile Vacutainer® system (Becton, Dickinson and Company, 1 Becton Drive, Franklin Lakes, NJ USA 07417) is opened and the blood collection needle inserted gently into the lumen of the vein at an angle of 15- 30^{o}, then the other end is attached to a Vacutainer® blood collection bottle. Blood flows freely into the bottle due to negative pressure. 2ml of blood for serum creatinine determination will be collected in a plain bottle and another 2ml will be collected in a S.S.T-bottle to be used for determination of the lipid profile.

After adequate blood has been collected, the tourniquet is released then the Vacutainer® needle is removed gently and an alcohol impregnated swab is applied at the site under pressure. Pressure is applied for a whole minute then the site is reassessed for continued bleeding. The area is dressed with a dry gauze and tape.

Appendix Six: Procedure for lipid profile

HDL CHOLESTEROL liquicolor is a homogenousenzymatic assay for the quantitative determination of HDL cholesterol.

Method

The assay combines two specific steps: 1st step chylomicrons,VLDL and LDL cholesterol are specifically eliminated and destroyed by enzymatic reactions. In the second step remaining cholesterol from HDL fraction is determined by well-established specific enzymatic reactions in the specific surfactants for HDL.

CHOLESTEROL liquicolor CHOD-PAP-Method Enzymatic Colometric Test for cholesterol with Lipid Clearing Factor (LCF)

Method

The cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine is formed from hydrogen peroxide and 4-aminophenazone in the presence of phenol and peroxidase.

TRIGLYCERIDES liquicolor GPO-PAP Method Enzymatic Colometric Test for Triglyceridess with Lipid clearing Factor (LCF)

Method: The triglycerides are determined after enzymatic hydrolysis with lipases. Indicator is quinoneiminine formed from hydrogen peroxide,4-amino-antipyrine and 4-chlorophenol under the catalytic influence of peroxidase.
Quality control: For all this quality control are run daily

Appendix Seven: Procedure for eye examination

The eye examination will take place in the eye unit. After sampling of the participants, the questionnaire will be filled from the diabetes clinic by the researcher or research assistants. The participant will be explained to that his/her eyes need to be checked in the eye unit. He/she will be escorted to the eye unit by the researcher/research assistant. First, the presenting visual acuity of the participant will be measured by the researcher. Visual acuity in this study will bedefined as number of letters read correctly without glasses if the participant did not have glasses or with glasses if they had them. Each eye will be tested separately at the 4M using Snellen charts in a well illuminated area. If a participant vision will be too poor to read any letter on the chart at 4M, then she/he will be tested at 1M, then counting fingers, hand movement, light perception and no light perception. The pupils of the participant will then be dilated with 1 drop of tropic amide 1% for a period of 10 minutes. The researcher will examine the macula, retinal vasculature and peripheral retina using a slit lamp and then an ophthalmoscope. The findings will be confirmed by an ophthalmologist before grading the participant's degree of DR using International Clinical DR Disease Severity Scale. If both eyes have features of diabetic retinopathy, the findings in the worse eye are used for grading.

Appendix Eight: Classification of Diabetic Retinopathy in the Early Treatment of Diabetic Retinopathy Study (ETDRS).

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Mild Non-Proliferative Retinopathy	At least one micro aneurysm, and definition not met for moderate non-proliferative retinopathy, severe non-proliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy
Moderate Non-Proliferative Retinopathy	Hemorrhages and/or micro aneurysms ≥ standard photograph 2A; and/or soft exudates, venous beading, or intra retinal micro vascular abnormalities definitely present; and definition not met for severe non-proliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy
Severe Non-Proliferative Retinopathy	Soft exudates, venous beading, and intra retinal micro vascular abnormalities all definitely present in at least two of fields four through seven; or two of the preceding three lesions present in at least two of fields four through seven and hemorrhages and micro aneurysms present in these four fields, equaling or exceeding standard photo 2A in at least one of them; or intra retinal micro vascular abnormalities present in each of fields four through seven and equaling or exceeding standard photograph 8A in at least two of them; and definition not met for early proliferative retinopathy or high-risk proliferative retinopathy
Early Proliferative Retinopathy (i.e., proliferative retinopathy without Diabetic Retinopathy Study high-risk characteristics)	New vessels; and definition not met for high-risk proliferative retinopathy
High-risk Proliferative Retinopathy (proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics)	New vessels on or within one disc diameter of the optic disc (NVD) ≥ standard photograph 10A (about one-quarter to one third disc area), with or without vitreous or pre-retinal hemorrhage; or vitreous and/or pre-retinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ one-quarter disc area