Factors associated with diabetic retinopathy among patients diagnosed with type 2 diabetes in Bangladeshi Population

M.Phil. Thesis

Photo by Deyan Georgiev

Rula Haddad

Factors Associated with Diabetic Retinopathy among Patients Diagnosed with Type 2 Diabetes in Bangladeshi Population

Academic dissertation submitted to

University of Oslo

by

Rula Haddad

in partial fulfilment for the award of the degree of

Master of Philosophy Degree in International Community Health

Supervisor:

Prof. Akhtar Hussein

Department of International Health

Institute of Health and Society

Faculty of Medicine

University of Oslo , Norway

Co supervisor:

Dr. Purabi Rani Deb Nath

Department of Ophthalmology

BIRDEM Hospital

Dhaka, Bangladesh

June 2016

Department of Community Medicine

Institute of Health and Society

Faculty of Medicine

University of Oslo , Norway

DECLARATION

I hereby declare that this Master's thesis is my own work, and it does not contain other people's work without this being stated; and does not contain my previous work without this being stated, and that the bibliography contains all the literature that I have used in writing the thesis, and that all references refer to this bibliography.

Oslo, June, 2016

Rula Haddad

To all the girls who dream and believe in education...

ACKNOWLEDGEMENTS

I would like to express my warmest thanks to all those who have helped me to complete this research; My Professors, colleagues, friends, and my family.

I am deeply indebted to my supervisor Prof Akhtar Hussein for opening up the opportunity for me to do the fieldwork in Bangladesh, which enabled me to gain the experience and knowledge of the Asian culture and life style. I extend my thanks to my local supervisor in Bangladesh, Dr. Purabi Rani Deb Nath for helping, organising and diagnosing the patients for my data collection. My appreciation goes to all the staff of BIEDEM for a good collaboration, and being helpful. Special thanks to the research assistant Sanjita Chaklader for helping to collect the data. Special thanks to all the patients who agreed to contribute to this study, and making it possible by being part of it.

My gratitude goes to the Institute of Health and Society, particularly to Professor Anne Karen Jenum for her valuable time, and helping in analysis. Many thanks to Terese, Course Coordinator for her collegiality, friendship, inspiration, and support. Special thanks to Mr. Ibrahim Mdala for his priceless support in statistical analysis.

I thank very much my parents for all their support and love, my precious sister Lamees for all the love, caring and support in the blue days. Special thanks to my best friend Sama from Palestine, for being amazing and understanding my frustration. Thank you dear Stian, for your support, encouragement, for the many ways in which you have contributed to making this study possible, for all our discussion and most of all for being there.

Without you all, I would not be able to accomplish this study

Thank you!

Oslo, June, 2016

Rula Haddad

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

BBS	Bangladesh Bureau of Statistics
BDT	Bangladeshi Taka
BIRDEM	Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CSME	Clinically Significant Macular Edema
CURES	The Channai Urban Rural Epidemiology Study Eye Study
DAB	Diabetic Association of Bangladesh
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
EDTA	Ethylenediamine Tetra Acetic Acid
ETDRS	Early Treatment Diabetic Retinopathy Study
FBS	Fasting Blood Sugar
GDP	Gross Domestic Product
HbA1c	Glycosylated hemoglobin
HDL	High Density Lipoprotein
HPLC	High Performance Liquid Chromatography
HTN	Hypertension
Kg	Kilo gram
LDL	Low Density Lipoprotein
LE	Left Eye
Mmol	Milli mole
Mmol/L	Millimole per Liter
MOHFW	Ministry of Health and Family Welfare
NGO	Non- governmental Organization
NPDR	Non Proliferative diabetic retinopathy
OR	Odds Ratio
OPD	Outpatient Department
PDR	Proliferative Diabetic Retinopathy
RA	Research Assistant

RBS	Random Blood Sugar
RE	Right Eye
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
SPSS	Statistical Package for Social Sciences
STR	Sight Threatening Retinopathy
TC	Total Cholesterol
TG	Triglycerides
UKPDS	United Kingdom Prospective Diabetes Study
VA	Visual Acuity
VI	Visual Impairment
WC	Waist Circumference
WESDER	The Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organization
WHR	Waist–to–Hip Ratio
WHtR	Waist Height Ratio

.

TERMINOLOGY

Diabetic Retinopathy (DR): Is one of the major micro vascular complications of diabetes that affects the microvasculature of the retina. It has different Types and grades depend on the progression and severity (1).

Non Proliferative Diabetic Retinopathy (NPDR): was diagnosed and graded by the presence of microaneurysms without any formation of abnormal new blood vessels, presence of cotton wool spots and venous bleeding. It can be mild, moderate, and severe (1).

Clinically Significant Macular Edema (CSME): Was identified when one of the subsequent appear:

1) Retina thicking at or within 500 microns or 1/3 disc diameter of center of macula.
2) Hard exudates at or within 500 microns at the center of the macula with adjoining retinal thickening
3) Retinal thicking is greater than 1 disc diameter in size that is within 1 disc diameter from the center of the macula (2).

Proliferative Diabetic Retinopathy (PDR): was diagnosed by the presence of new abnormal blood vessels on or in the region of the optic disc, vitreous hemorrhage or retinal detachment(1).

Indirect Ophthalmoscope: Is an instrument which constitutes a light attached to the head, in addition to a small handheld lens. It provides a wider view of the insider of the eye that allows a better view of the fundus of the eye, even if the lens is clouded. It is used for the peripheral viewing of the retina (2).

Fundus Photography: Is the creation of a photograph of the interior surface of the eye including the retina, optic disc and macula, usually used by trained medical professionals. Good instrument for monitoring progress of a disease or screening and epidemiology especially it gives documents as reference (2).

ABSTRACT

TITLE

Factors associated with diabetic retinopathy among patients diagnosed with Type 2 diabetes in Bangladeshi Population

BACKGROUND

Diabetes mellitus (DM) is associated with micro vascular complications, such as diabetic retinopathy (DR). DR is a serious problem that is well characterised by impaired vision; a condition known as sight threatening retinopathy (STR).The incidence and prevalence of STR have been noticed and well recognised in developed countries. However, there was only one national survey that emphasised on causes of visual impairment and blindness among adults in Bangladesh, but it revealed that DR is not the main cause for blindness or visual loss among this population. No other studies have been conducted in Bangladesh that estimates the magnitude of STR, and the impact of prognostic indicators on STR, visual impairment and blindness. Moreover there is no study that identifies the determinants of severity and progression of DR among early and late diagnosed type 2DM.

AIM

To assess the determinants of progression of diabetic retinopathy(DR) among diagnosed type 2 diabetic, and to assess the proportion of sight threatening and visual impairment among type 2 diabetes patients who attended BIRDEM hospital in Bangladesh.

METHODOLOGY

A cross sectional study was conducted in outpatient ophthalmic clinic at BIRDEM, Dhaka in a period from 25th September 2014 till 17th November 2014. Dilated color fundus photography was performed in all patients who have type 2 diabetes, and were over 30 years old .Those who was showing some degree of retinopathy were included. DR was classified according to the changes in the worse eye into three stages based on EDTRS classification as the following: 1) Patients with Non-Proliferative Retinopathy (NPDR) 2) Patients with CSME stage (in the presence of NPDR) 3) Patients with PDR stage (in presence or absence of CSME). Sight

threatening was defined as the presence of CSME, or PDR in either or both eyes. Visual Acuity (VA) was classified following the International Statistical Classification of Diseases (ICD) and World Health Organisation (WHO) . VA was classified as normal 6/6 to 6/18, moderate visual impairment (<6/18 to $\geq$ 6/60) in the better eye, and severe visual impairment (<6/60 to $\geq$ 3/60) in the better eye.

Data on socio-demographic characteristics, anthropometric measures and blood pressure were obtained from patients meeting the eligibility criteria. Biochemistry blood test was recorded from the patient book file

the patient book file

RESULTS

Two hundred and fifty seven patients (110 female, 147 men) with type 2 diabetic were included in the study. Diabetic retinopathy was distributed as follows; NPDR (36%), CSME (43%), and PDR (21%). The proportion of patients with STR and visual impairment (moderate and severe) were 64% and 56.4% respectively. . Severe visual impairment (VI) was observed in 11.7% of the cases. Systolic blood pressures (SBP), urban residency, were associated with VI. Limited studies have evaluated BMI and VI; interestingly, high BMI (over weight) was inversely associated with VI in this study. The risk of STR was associated with age, HDL, LDL ($P < 0.05$). The median time to STR onset was estimated at 17 years for females, and 15 years for men. DR prognosis was associated with SBP, female gender, urban residency. A surprising result was that BMI particularly over weight inversely associated with the development of PDR versus NPDR, CSME combined. HbA1c was not significantly associated with STR, visual impairment or progression of DR

CONCLUSION

Our study showed that the prevalence of visual impairment among DR patients was much higher than the national estimate of 13.8%. In resource limited countries like Bangladesh, regular screening for diabetic complications should be supported fully by government health institutions if the prevalence of STR and visual impairment are to be reduced substantially. The support should be extended to health awareness programs on modifiable causes of diabetes.

KEY WORDS

Diabetic retinopathy, Non proliferative, Proliferative, CSME, sight threatening, visual impairment.

1

INTRODUCTION

1.1 A BRIEF COUNTRY PROFILE

1.1.1 *Geography*

Bangladesh is situated in south Asia, between India and Myanmar, on the biggest delta on Earth. Most of the country is low and flat, only some parts of the country have small hills that are more than 12 meters above the sea level. Thus, one third of the state is flooded every year during the normal monsoon season. The total area is 144,000 Km^2. The climate is semi-tropical with high temperatures and humidity in summer that last from March to June, and a mild winter from October to March. The warm and rainy monsoon season last from June to October (3).

Bangladesh has a good deal of natural resources such as the natural gas, clay, glass sand, lignite coal, and also produce many agriculture products such as rice, tobacco, tea, straw, spices, vegetables and tropical fruits like coconut and mangoes. It has some famous industries as well, such as the cotton, sugar, leather, cement, fertilizer and fish (4).

1.1.2 *History*

Britain dominated the South Asian region in the 18th century, and Bangladesh was part of the British Indian at that time. When India got its independence in 1947, the Bengal area was split into two regions; East Bengal and West Pakistan, which became the new state of Pakistan. This status lasted for twenty four years, and in 1971, East Bengal became an independent nation and is now known as the People's Republic of Bangladesh. Its capital city is Dhaka (4).

1.1.3 *Population*

According to the result of the population and housing census that was conducted in March 2011, the total population was around 142,319 million, with a population density 964 inhabitants

Figure 1: Map of Bangladesh. Source: http://www.mapsofworld.com/bangladesh/

per square kilometer. By 2011, the annual growth rate had decreased to 1.37% from 1.58% in 2001. Today, Bangladesh remains one of the most densely populated countries in the world. Bangladesh is an Islamic state with 89.5% Muslims, 9.6% Hindus and 0.9% Christians. Youth ($\leq$25 years) make up 60% of the population and persons aged $\leq$65 years make up 5%. Seventy-two percent of the populace lives in rural regions (5; 6).

The literacy rate is 56.9%, with 61.3% of the males being literate compared to 52.2% of the females among those who are at least 15 years old (5). The official language in Bangladesh is Bangla, which is spoken by 98% of the population.

1.1.4 *Economy*

Bangladesh has made prominent progress in the economic sector since independence in 1971. Despite political instability and insufficient infrastructure including poor power supplies, the economy has grown by 6% per year since 1996. The agricultural sector contributes 17.2% of the nation's GDP while industry and service sectors contribute 28.9% and 53.9% respectively (6). In 2013, the average GDP per capita income was about $2.10, which gave Bangladesh number 194 in the world. The disparity between rich and poor is high, and this inequality is thought to be one of the causes for a slow economic growth. In addition, corruption, delays in exploiting energy resources (natural gas) and unstable political situation also contributes to a slow economic growth (5).

Currency: Bangladeshi Taka (BDT)

The average exchange rate for May 2016 [a]:

1 USD = 78.5202 BDT

a Source: `http://www.xe.com`

1.1.5 *Life style*

Cases of food consumption vary at individual household level and at regional level according to socio-economic status. Nevertheless, rice is the main food and is eaten almost at every meal as a tradition in both urban and rural regions. Food in Bangladesh is so spicy and fried with oil most of the time. According to the regional data, Bangladeshi consumes food rich in carbohydrates and also sweets more than they consume fruits and vegetables (7). The high prices could be one reason, but also it is more linked to civilisation and lifestyle. People in Bangladesh consume less protein and fibers but more carbohydrates. Dairy products and meat are consumed occasionally in small amounts. Fried fish with rice is one of the traditional dishes (8).

According to the nutrition surveys in 2005, anaemia prevalence is high especially among pre-school children (68%) and adolescent girls (40%) in rural areas and a bit less in urban areas (9). The high prevalence of stunting among children below 5 years old (20%) at the state level reflects a deficiency of micro-elements such as vitamin A, folic acid, zinc, and malnutrition (10).

People in Bangladesh like to sleep after lunch and immediately after a late dinner as a common tradition like other Asian countries.

Physical activity is not part of the routine daily life; the people do not like to do extra physical exercise other than the requirements of their occupation activity. Women spend all their energy doing household chores, especially in rural areas where there is a great demand of activities within and around the home. Urbanization and rapid socio-economic transition has affected the lifestyle of the people in Bangladesh, which in turn has resulted in decreased physical activity and increased sedentary lifestyle of working (7).

1.1.6 *Health Care System*

According to the World Health Organization (WHO) report in 2010, the expenditure on health-care was 3% of the Gross Domestic Product, but only 34% of the total health expenditure is covered by the government and the rest is covered as out of pocket. The Ministry of health and family planning (MOHFW) has the responsibility for the health sector and policy planning. Inspite of MOHFW taking the responsibility of the health care services, the non-governmental organizations (NGOs) and voluntary social organizations (VGOs) dominate the provision.

The health system faces many challenges such as shortage of human and material resources, lack of public health facilities, lack of comprehensive wellness policy, political instability and lack of dedication. Nevertheless, Bangladesh has demonstrated improvement in reaching the Millennium Development Goals (MDGs) especially MDG 4 and MDG 5 (11). Table (1) shows the amount of sample vital registration of 2011 (11).

Infant Mortality Rate (IMR)	43 deaths per 1000 live births
Children Mortality Rate (CMR) (under 5)	44 deaths per 1000 children
Maternal Mortality Rate (MMR)	194 per 100,000 live birth
Life Expectancy at birth	66 years
Vaccination Coverage	87.5%

Table 1: Adapted from The Health System in Bangladesh: Challenges and Opportunities, 2014

Improving the health system in Bangladesh requires massive efforts and substantial tasks to decrease the inequality and inequity between peoples and gender in order to access the basic health system, and to invest in the available limited resources while rebuilding the system.

Bangladesh has experienced epidemiological transition, which puts extra burden upon the health and the economic system. This burden requested more extra efforts to eliminate both the communicable diseases such as water born infectious diseases and the non-communicable diseases such as diabetes and hypertension.

This epidemiological transition could be as a consequence of urbanisation that leads to changing lifestyle, eating habits, sedentary life, smoking, and lack of exercises, in addition to the environmental factors such as lack of hygiene, sanitation, insufficient food and stress.

Bangladesh government and non-governmental health organisation have identified two top non communicable diseases as major public health problems; diabetes and cardiac diseases. In order to tackle these diseases, cooperation between the surveillance systems was implemented, and country policies were formulated.

Diabetic Association of Bangladesh (DAB) has led up the surveillance of Diabetes mellitus countrywide (12). DAB, a non-profit medical NGO, was established in 1956 and started its first clinic for out-patients in Dhaka in 1957.This clinic has become a big medical institution in the country and now known as Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) (12).

1.2 DIABETES MELLITUS

Diabetes Mellitus (DM) is a chronic, metabolic disorder with multiple aetiologies that results in abnormal glucose control. This can be due to defects in insulin secretion, insulin action or both. It has become an emerging epidemic disease that impacts over 8.3% of the population worldwide (11). According to the International Diabetic Federation (IDF), the total number of diabetics will rise from 387 million in 2014 to 592 million in 2035. The most affected age group is 40-59 years, and 77% are living in low and middle income sectors. South Asian countries are experiencing significant morbidity and mortality from complications of diabetes and this causes a significant health and economic implications (13).

Research has shown that 15% to 20% of South Asians are likely to develop type 2 diabetes mellitus, regardless of their living area compared to 2% to 5% of Caucasians (14).

1.2.1 *Existing diabetes health care services in Bangladesh*

Currently, the government health provision in Bangladesh concentrates more on communicable diseases and so diabetic care is provided mainly by NGOs especially DAB which offer specialist clinics and tertiary specialist hospitals. The association implements its program mainly by the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) which has a large network of specialist diabetes across Bangladesh, and has a main hospital in Dhaka that plays a unique role in providing care for diabetic patients. Only at BIRDEM clinic in Dhaka, do patients receive a routinely regular complete check up rather than just blood glucose level monitoring (15). At present, more than 3500 registered patients receive health services from BIRDEM OPD every day (16).

1.2.2 *Diabetes Complications*

Complications of diabetes can be divided into macro and micro vascular disease (7). The macro vascular complications consist of coronary disease and cerebrovascular disease. The micro vascular complications include neuropathy, nephropathy, and diabetic retinopathy. Diabetes has many effects on the eye, but Cataract and diabetic retinopathy (DR) are the most considerable cause of optical impairments and blindness. Diabetic people have 25 times more chances than the general population to become blind (7). In industrialised countries, DR is considered a leading cause of blindness onset, and also a common cause of blindness in middle income countries (17).

1.2.3 *Diabetic Retinopathy*

Diabetic Retinopathy occurs in both type 1 and type 2 DM. It is present in all individuals with type 1 and in more than 60% in type 2. This complication is likely to occur 15-20 years after being diagnosed with DM, either type 1 or type 2 (18). The proportion of blindness from DR ranges from 0% in most African countries, 3-7% in most South East Asian countries, to 15-17% in rich states of America, Europe, and the Western Pacific (18).

Visual impairment as a result of DR has a major influence on patients' quality of life, which affect their capability of managing their daily life and their disease which can influence negatively on the incidence of other diabetic complications, and their life expectancy (19). DR is one of the leading causes of blindness in the developing and developed world that is associated with

damage to the small blood vessels in the retina resulting in loss of vision. The World Health Organisation (WHO) has reported that DR is responsible for about 5% of the global cases of the blindness (20). The prevalence of DR in type 2 Diabetes varies among and between the developed and developing countries. It ranges from 4% to 40% (21).This diversity can be due to different diagnostic technique for DR, or due to different populations, demographic, or due to different methodologies and studies, or different time of diagnosis for diabetes.

There are mainly two forms of DR; the less rigorous form; Non Proliferative Retinopathy (NPDR), and Proliferative Retinopathy (PDR). NPDR is asymptomatic, where the vascular permeability increased, contributing to superficial and deep retinal haemorrhages, hard exudates, and macular edema that decrease the nourishment supply to the retina. It can be mild, moderate or severe. PDR is associated with an increase of new vessels on the retina that is easy to go down and bleed, which may lead to vitreous or retinal hemorrhage, which cause sudden loss of imagination, or may cause traction to the vitreous, or neovascular glaucoma (22).

Diabetic macular edema (DME) which is the thickening of the macula caused by more permeable vessels that can arise at any stage of DR, and is believed to be the most common example of visual loss in NPDR. This condition is connected up with the duration and type of diabetes and the grade of DR. Clinically Significant Macular Edema (CSME) is the more severe form requiring immediate intervention (23).

1.2.4 *Diagnosis and Classification*

According to the Early Treatment Diabetic Retinopathy Study (EDTRS), the gold standard for identifying DR is the seven standard field stereoscopic colour fundus photography (24). ETDRS is a modification of the original Airlie House Classification and the Diabetic Retinopathy Study (DRS) (24; 25). This classification is used for a full disease classification and it is not for population screening.

DR classification is founded on the absence or presence of abnormal new vessels which is known as NPDR or PDR respectively. NPDR can be mild, moderate or severe based on the number of microaneurysms seen on fundoscopy.

ETDRS defined CSME as a presence of retinal thickening with or without hard exudates within 500μm of the fovea, or when there is a zone of edema that is larger than the optic disk at the distance of one optic disk diameter. CSME is a serious condition in which the vision of the diabetic patient is endangered by DR, but the patient can still see well (26). When DR affects the macula lutea, which is the area that responsible about the central vision, then it is defined as

diabetic maculopathy. Diabetic maculopathy can occur due to edema or, as a result of occlusion in the capillary system which is known as ischemia or as a complication of ischemia and edema. Ischemic maculopathy is not treatable and it gives poor prognosis for visual acuity (27).

1.2.5 *Screening Protocols*

Current screening protocols suggest that type 1 diabetic patients have to be examined by ophthalmologist for dilated fundus exam within 5 years of diagnosis (28). Diabetic type 2 patients have to perform dilated fundus exam at the time of diagnosis of diabetes, as many patients got the disease without being aware of the symptoms. Moreover, some studies have found that 20% of type 2 DM had already developed DR when they are diagnosed (18). Therefore, the follow up fundus examination should be done at least yearly if there are no abnormal findings. However this protocol is not applied in the developing countries for many reasons such as lack of human and material resources like ophthalmologists, machines and lack of available protocols (28).

1.2.6 *DR in South Asia*

It has been reported in many studies that the prevalence of diabetes in Asians could be as higher as four times than people from Caucasians origin (29) .Similarly, the comparison of diabetic complications on the basis of the prevalence of diseases between Asian and Caucasians would show a greater difference. DR prevalence is different, even within and among Asians themselves. Population based studies from India found that the range of prevalence is from 12.2% to 17.6% (30; 31), whereas another population study based on screening subjects over 30 years from Pakistan mentioned that DR prevalence was 27.43% of diabetics (32). Yet another population study based on screening subjects, also in Pakistan reported DR to be 15.3% of the diabetics (33). However, studies from China revealed that DR ranges from 27. 9% to 43.1% of the diabetics Chinese adults (34; 35).

1.2.7 *Situation in Bangladesh*

The trend of diabetic retinopathy is expected to increase in Bangladesh, as a consequence of increased diabetes prevalence in the country. However there are very few studies conducted at the national level to highlight the prevalence of DR among known and newly diagnosed diabetes.

A population based study conducted through screening in the rural community to study the prevalence and the risk factors among this population identified that the prevalence of DR among diabetic was 21.6 % (36). Another retrospective cohort study conducted in a tertiary hospital by following the patients' records for 15 years revealed that the accumulative incidence of DR was 50.6%. These studies reflect the importance of conducting reliable epidemiological studies that can be the baseline for the national policy makers for planning programs for eye care. Moreover, established risk factors such as DM duration, the control of serum glucose level, hypertension and hyperlipidemia have not been associated with the progression and severity of DR, but are known risk factors for developing DR among diabetic population.

1.2.8 *Justification of the study*

Early onset type 2 DM may affect the development of DR at a relatively younger age. DR is a serious problem that is well characterised by impaired vision; a condition known as sight threatening retinopathy (STR).The incidence and the prevalence of STR have been noticed and well recognised in developed countries (18; 37). However, there was only one national survey that emphasised on causes of visual impairment and blindness among adults in Bangladesh, but it revealed that DR is not the main cause for blindness or visual loss among this population. There was no other study conducted among Bangladeshi population that estimates the magnitude of STR and the impact of factors on the probability of STR, visual impairment and blindness. Moreover, there is no study that identifies the determinants of severity and progression of DR. To bridge the gap in the literature, this study was conducted.

1.3 RESEARCH OBJECTIVES

1.3.1 *General objectives*

To assess the determinants of severity and progression of DR among diagnosed type 2 diabetic outpatients in Dhaka, Bangladesh.

1.3.2 *Specific objectives*

(i) To determine the clinical characteristics of patients presenting with STR

(ii) To assess and describe visual impairment among diagnosed DR.

(iii) To identify the different characteristics of female patients and male patients diagnosed with DR, ST, and VI among diagnosed type 2 DM

2

METHODS

2.1 STUDY SETTING

The study was done in the outpatient Ophthalmology department at BIRDEM, the central Institute of the Diabetic Association of Bangladesh in Dhaka, in a period from 25th September 2014 till 17th November 2014. BIRDEM has about 700 bed inpatient tertiary hospital, with modern medical studies.

2.2 STUDY DESIGN

Due to limited resources and time, a cross sectional design was selected to acquire data regarding factors associated with DR in patients with known type 2 DM.

2.3 SAMPLE SELECTION

2.3.1 *Inclusion Criteria*

Patient over 30 years old, known as diabetics, or newly diagnosed type 2 diabetes (already on oral hypoglycemics, or insulin) coming to outpatient ophthalmic department (OPD) for routine check up with or without complaining of decreased vision or any other ocular symptom.

Patients diagnosed with DR regardless of severity after performing the regular eye examination and the fundus photographs.

Patients who give informed consent to participate in the study.

2.3.2 *Exclusion Criteria*

Patients with type 1 diabetes, gestational diabetes or patients who were pregnant at the time of the study. Patients who have no signs of any type of DR after fundus examination.

2.3.3 *Sample size calculation*

The sample size was based on having a statistical power of 80% in order to detect a difference in prevalence of about 4.6% and a critical level of 5% as given in the formula below;

$$n = \frac{Z^2_{\alpha/2} pq}{d^2} = \frac{1.96^2 \times 0.167 \times 0.833}{0.046^2} = 252$$

Where α is the desired significance level (typically 1.96 for a 95% confidence interval).

Here, p is the prevalence of diabetic retinopathy, which in Bangladesh is estimated at 16.7% (36), d is the difference in prevalence and is the probability of making a type I error, giving a $Z_{\alpha/2}$ = 1.96 for a 95% confidence interval. Therefore, the study required a minimum of 252 participants. Therefore, we decided to match the sample size to the limited time and budget and so we decided to include 260 patients.

The number of patients who refused to participate (non participants) was 3 (1.2%) giving a response rate was 98.8%. Therefore, 257 patients participated in the study; answered the questionnaire, performed the clinical and the anthropometrical measurements and completed the comprehensive eye examination.

2.3.4 *Pre-testing (piloting)*

The pre-testing was accomplished to identify potential problems and to examine the applicability of the questionnaire. Therefore a small pilot study was done on 5 patients fulfilling the inclusion criterion. There were no misunderstandings so no changes were made after pilot testing.

2.3.5 *Selection and training of research assistants*

As the study involved a questionnaire and clinical examination, at least one research assistant was needed to help the main researcher in data collection. A female medical doctor who had finished her internship at BIRDEM was recruited. Three days training (both theoretical and practical) was given .The training focused on the demonstration of the questionnaire, communication skills and ethical issues.

2.3.6 *Research instruments*

A structured questionnaire (Annex B) was developed based on the literature. It was initially developed in English, then translated to Bengali language by a colleague who also has a good experience in public health, and also was revised by BIRDEM committee of research before using it. It was then translated back to English by another person who was not part of the research to check for the internal validity of the questions, and to be modified after pre testing. The questionnaire constituted of five parts: 1) Socioeconomic and general information; 2) Medical history; 3) Anthropometrical measurements; 4) Clinical measurement; and 5) Biochemical measurements

2.3.7 *Anthropometric measurements*

Anthropometric measurements including height, weight, waist and hip circumferences were measured from the participants of this study. The measuring of the waist and hip circumferences were done in nearest centimeter, with a non stretchable measuring tape. Waist circumference was taken from the midpoint between the iliac crest and lower margin of the ribs. Hip circumference was measured at the symphysus pubis. The measurements performed while the patients were standing and breathing normal. Waist to Hip ratio (WHR) was calculated from the measurement of the waist and hip. The measurement of the body weight was done to the nearest 0.1 kg using a Sohenle mechanical weighing scale (Soehnle—Waagen GmbH and Co.KG, Wilhelm-Soehnle 2, D-71540 Murrhardt/Germany). The height was measured to the nearest 0.5 cm using a rigid measure against a vertical wall, where the patients stand upright without shoes. Body Mass Index (BMI) was calculated as the ratio of weight (kg) over the square of height (m^2). The measurements performed in all the patients by the same research assistant.

2.3.8 *Measurement of Blood Pressure*

Blood pressure was measured in a sitting position by a standard mercury sphygmanometre and a suitable sized cuff while the arm supported on a table. The measurement was taken from all the patients by the same research assistant.

2.3.9 *Biochemical Measurement*

The Diabetic Association of Bangladesh has developed a diabetic guide book given to all diabetic patients. The books contain information regarding patients medical conditions from the date they were registered to their present status. Information on clinical and laboratory findings and the treatments that the patients received are also found in these guide books. Therefore, all the biochemical measurements, which include FBS, RBS, HbA1c, Creatinine, Urea, Lipid Profile (HDL, LDL, TG, CH) were extracted from these diabetic guide books and used as part of this study. All the biochemical measurement was analyzed according to BIRDEM laboratory routines methods, where Glycosylated hemoglobin (HbA1c) was analyzed by high performance liquid chromatography (HPLC). The Automatic Analyser (Hitachi Ltd, Japan) was used for analyzing Triglycerides (TG), Total Cholesterol (TC) and High Density Lipoprotein (HDL), while the reagents were from Randox Laboratories in United Kingdom. Low density Cholesterol was calculated as Friedewald (1972) Formula: LDL = TC - HDL - TG/5.0 *mg/dl* (38). The estimation of serum creatinine was done by alkaline picrate methods and by means of reagents of Randox Laboratories, UK. Urea was also analyzed by Automatic Analyser. All the Biochemical measurement was up to date, and the oldest was done 3 months before the study, therefore all the biochemical measurement was recorded according to the last record which was done the latest 3 months before the study.

2.3.10 *Eye Examination*

This procedure was done completely according to the hospital policy for checking the eyes of diabetic patients ,therefore all patients went through comprehensive eye examination that starts by testing the visual acuity by using Snellen chart at a distance of 6 meters. Presenting and best visual acuity was recorded separately for each eye (39). Slit lamp examination (Topcon Corp, Japan) was performed to document any abnormalities in the anterior segment. Intraocular pressure was measured with Schoitz indentation tonometer (Schoitz, John Weiss &Son Ltd,

London, UK) before dilating the pupils. The retina was examined after mydratics drops were applied to each eye (one drop of tropicamide 0.5% and one drop of phenylephrine 2.5%) by using binocular indirect opthalalmoscope (keeler Instruments Inc, PA, USA) to detect any abnormalities, and then the patients were asked to perform the fundus photography for both eyes. Topcon TRC.50EX® retinal camera with Nikon D5000® 12.3 megapixel digital camera was used to confirm the diagnosis, and to ensure validation of the retinopathy. This examination was done by senior ophthalmologist and retina specialist. The retina was then graded by severity of DR according to the modified Early Treatment Diabetic Retinopathy Study Classification System (EDTRS) in the worse eye. Patients with no signs of DR were excluded as per study protocol.

According to the hospital policy all the diabetic patients have to do the retinal photography. If the patient had done this photo within the last 3 month,it was accepted ,and no new photo was done.

2.4 VARIABLES

2.4.1 *Independent variables*

2.4.1.1 *Socio-demographic variables*

Age was collected in years, then categorized into 5 age groups; 30-39 years, 49-49 years, 50-59 years, 60-69 years, 70 years and above. Marital status had 5 options in the questionnaire: married, unmarried, separated, divorced, and widowed. Neither of the patients was divorced nor separated, so we kept 3 options married, unmarried, and widowed. Level of education was collected by asking about the total years of education, then categorized into 8 levels, according to the educational system in Bangladesh; illiterate, primary (1-5), junior (6-8), matriculation (9-10), intermediate (11-12), graduation (college, university), master and doctorate. Residential area was determined from 3 options: urban, rural, semi urban, and then rural and semi rural was combined together as one variable because they were almost similar. The monthly household income was collected in Bangladeshi Taka, and categorized into low ($\leq$ 25000 BDT), and high ($>$ 25000 BDT).Smoking was assessed by asking the patients if they were smokers or not. All patients who smoked were asked about their preferences (cigarette, pipe, cigar, others). Only cigarette smokers were found in this study.

2.4.1.2 *Anthropometrics*

Asian BMI criteria were performed to define overweight and obesity in this group. BMI $\geq$23 kg/m^2 is considered as overweight, and $\geq$25 kg/m^2 is considered obese (40). Abdominal obesity was evaluated by waist to hip ratio; cut off points taken at 0.8 for females and 0.9 for males (41). The waist height ratio was calculated; cut off points for both males and females were >0.5.

The cut off points for the waist circumference were considered at $\geq$80 cm for females, and $\geq$90 cm for male

2.4.1.3 *Clinical Measurement*

Hypertension was defined as SBP $\geq$ 140 $mmHg$ and DBP $\geq$ 90 $mmHg$ (42).

2.4.1.4 *Biochemical measurement*

There are many blood tests to assess how well diabetes is controlled, but three tests were chosen from the diabetic guide book of the participants; glycosylated hemoglobin (HbA1c), fasting Blood Sugar (FBS) and random blood Sugar (RBS). All the biochemical cut offs followed the American diabetes Association guidelines (38). HbA1c the uncontrolled glucose level was identified $\geq$7.0 %, FPG was defined $\geq$7*mmol/l*, and RBS was defined $\geq$11.1*mmol/l*. The abnormal lipid profile was considered to be there when the TC was >200 *mg/dl*, TG was >150 *mg/dl*, LDL was $\geq$ 100 $\geq$ *mg/dl*, HDL was < 40 mg /dl for men and 50< *mg/dl* for women. If the patient has a cardiac problem, LDL was > 70 *mg/dl*. Serum creatinine was considered abnormal if the creatinine was >1.4 mg /dl for males and >1.2 mg /dl for females. Urea was considered abnormal if the reading was >50 *mg/dl*.

All the Biochemical measurement was up to date, and the oldest was done 3 months before the study, therefore all the biochemical measurement was recorded according to the last record which was done the latest 3 months before the study.

2.4.2 *Dependent variables*

2.4.2.1 *Diabetic Retinopathy*

Patients were divided according to the most severe changes in the worse eye based on the modified Early Treatment Diabetic Retinopathy Study Classification System (EDTRS) into the following three categories (38):

Patients with Non Proliferative Diabetic Retinopathy (NPDR) stage.

Patients with Clinically Significant Macular Edema (CSME) stage (in the presence of NPDR).

Patients with Proliferative Diabetic Retinopathy (PDR) stage (irrespective of presence or absence of CSME).

2.4.2.2 *Sight–threatening–retinopathy (STR)*

Patients with NPDR were classified as non-sight threatening retinopathy (NSTR). Patients who had CSME or PDR in either or both eyes were classified as sight-threatening- retinopathy.

2.4.2.3 *Visual Impairment*

Visual Acuity (VA) was classified following the International Statistical Classification of Diseases (ICD) and World Health Organization (WHO) (43).

VA was classified as normal (6/6 to 6/18), moderate visual impairment (<6/18 to $\geq$6/60) in the better eye, and severe visual impairment (<6/60 to $\geq$ 3/60) in the better eye.

2.5 DATA COLLECTION PROCEDURE AND PRACTICAL EXPERIENCE IN THE FIELD

2.5.1 *Procedure*

All patients were referred by the Ophthalmologist after receiving their treatment to the RA. This was done to ensure that the patients will participate in the study by their own will and not as part of their treatment routine. This also made our work systematic as the patients came to us having completed VA test, eye examination, fundus photographs and had been assigned the grade of the

DR severity. The research assistant explained to the patients about the project and then obtained an informed consent from each patient. The RA then interviewed the patients, recorded the biochemical data from the patients–Guide books, measured their waist, hip, height, weight and BP. The researcher was following each patient and after detailed reading of the necessary data, an ID number was given to each completed questionnaire. The following flow chart (Figure 4) illustrates the procedure of data collection.

2.6 ETHICAL ISSUES

Approval was obtained from the Ethical Committee in Norway and also from The Diabetic Association of Bangladesh (DAB) before the initiation of the study. The study was done in accordance with the Declaration of Helsinki. The participants were informed about the purpose of the study and its objectives in Bengali language. There were also informed that they could withdraw from the study at any stage and that they had the right to refuse answering any of the questions they did not want to. No undue incentive was given to any patient. They volunteered and gave verbal and written informed consent prior to being included in the study. The clinical examination was done carefully to avoid any discomfort to them. All the findings were kept confidential. Each patient was given an ID number.

2.7 DATA HANDLING

The Statistical Package for Social Sciences (IBM SPSS version 22) and Stata 13 for windows were used for data analysis.

2.8 STATISTICAL METHODS

Descriptive statistics in the form of proportions/ percentages of subjects with different forms of diabetic retinopathy were estimated as shown in Table 1. Graphical approaches in the form of bar graphs, linear plots and pie charts have also been used to summarize the data. Analysis of variance (ANOVA) was used to test the mean differences of continuous data such as blood parameters in different groups. The study also established the strength of relationships between LDL, HDL, Cholesterol and TG after Controlling for the Type of Retinopathy using scatter plots and Pearson correction coefficients.

The outcome variable DR is ordered with three categories; NPDR(less severe), CSME (moderate severe), and PDR (most severe).To investigate the factors that are associated with severity of DR, an ordered logistic regression model was fitted to the data. One of the main assumptions underlying the ordered logistic regression model is called proportional odds assumption. This states that the relationship between each pair of DR categories is the same. For example, NPDR versus CSME and PDR combined is the same as NPDR and CSME combined versus PDR. Model testing showed that the proportional odds assumption was met. The modeling process proceeded in two steps; first, univariate ordered logistic regression models were fitted to the data. Secondly, all variables that were significantly associated with severity of DR together with variables that were clinically relevant were used in the multiple ordered logistic regression model.

Survival analysis in the form of Kaplan-Meier plots and Cox regression model were performed in order to understand the median time to onset of ST and associated factors. The time to onset was determined retrospectively from the moment the patients were diagnosed with diabetes up to the current study time.

2.9 HANDLING OF MISSING DATA; MULTIPLE IMPUTATIONS

Missing data identification analyses was done on 16 variables to identify at least 0.01% of data missing to be selected for multiple Imputations using IBM SPSS version 22 for windows .The analysis yielded that 8% values were found missing while 13.6% of the cases were complete. The percentages of missing data for all the 16 variables are shown in Figure 2 and 3, and Table 2 shows the pattern of missing data. The missing data pattern showed that the data was Missing at Random (Figure 3 showing isolated islands of missing data suggesting the ‘missing at random pattern’). Therefore, Markov Chain Monte Carlo (MCMC) method of multiple imputation (MI) procedure was used to impute missing values. A total of five iterations were done to generate the pooled results for the missing values.

After Multiple Imputations for missing variables, the values with their mean and standard deviations along with their comparison with non–imputed data (analysis including missing values) are shown in Table 3.There was no statistically significant difference observed in the values before MI and Pooled values after MI.Therefore all the descriptive results for the 257 patients are shown using pooled values (after MI).

Table 2: The Variables and corresponding percentages of missing data (in order of highest missing percentage first

S. No.	Variable	Valid Values	Missing
1	Urea mg/dl	80	177
2	Creatinine mg/dl	251	6
3	Total Serum Cholesterol mg/dl	252	5
4	Triglycerids mg/dl	251	6
5	HDL mg/dl	251	6
6	LDL mg/dl	250	7
7	HbA1c %	137	120
8	FBS mmol/L	256	1
9	RBS mmol/L	256	1
10	Waist Circumference cm	257	0
11	Hip Circumference cm	257	0
12	Weight cm	257	0
13	Height cm	257	0
14	BP Systole mmHg	257	0
15	BP Diastole mmHg	257	0
16	Duration of Diabetes years	257	0

Table 3: Comparison of Imputed and Non-Imputed Data (n=257)

Variable	Mean (SD) before MI	Pooled mean after MI	P-value
Urea mg/dl	35.15 (17.26)	35.36 (16.68)	0.91
Creatinine mg/dl	2.21 (13.60)	2.21 (13.52)	1
Total Serum Cholesterol mg/dl	175.77 (51.35)	176.68 (52.97)	0.8
Triglycerids mg/dl	174.35 (113.03)	176.95 (118.29)	0.75
HDL mg/dl	41.11 (17.18)	42.58 (31.78)	0.47
LDL mg/dl	111.05 (39.14)	111.00(43.01)	0.98
HbA1c %	1.87 (0.34)	1.85 (0.36)	0.53
FBS mmol/L	9.50 (5.92)	9.50 (5.91)	1
RBS mmol/L	13.08 (7.76)	13.08 (7.74)	1
Waist Circumference cm	92.43 (9.01)	92.43 (8.99)	1
Hip Circumference cm	95.81 (10.96)	95.81 (10.95)	1
Weight Kg	64.06 (13.81)	64.06 (13.80)	1
Height cm	155.77 (13.07)	155.77 (13.05)	1
BP Systole mmHg	128.01 (14.43)	128.01 (14.41)	1
BP Diastole mmHg	80.35 (8.44)	80.35 (8.42)	1
Duration of Diabetes Years	14.44 (7.12)	14.44 (7.11)	0.98

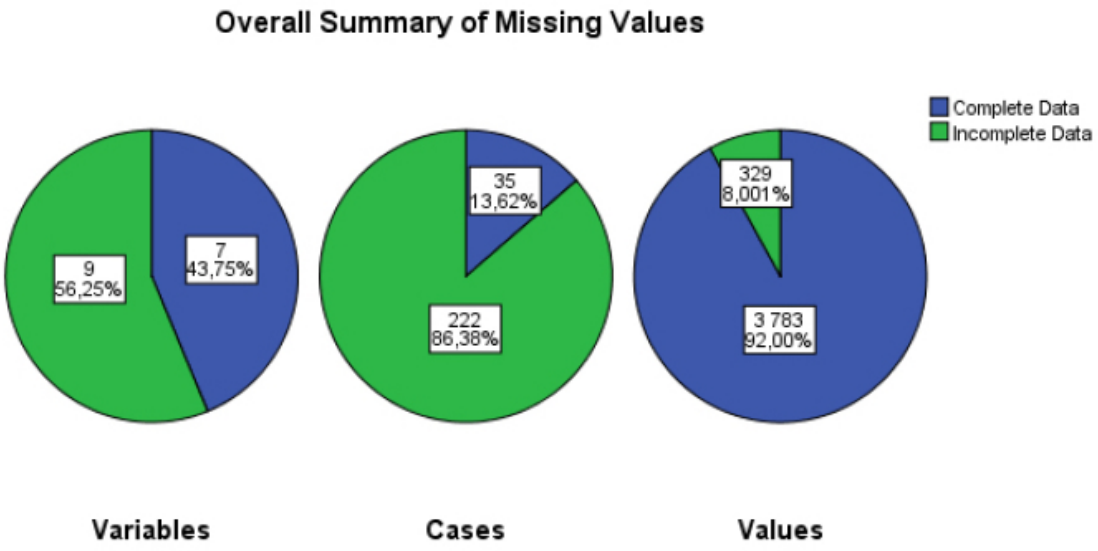

Figure 2: Percentages of missing data according to Variables, Cases and Values for all patients (n=257)

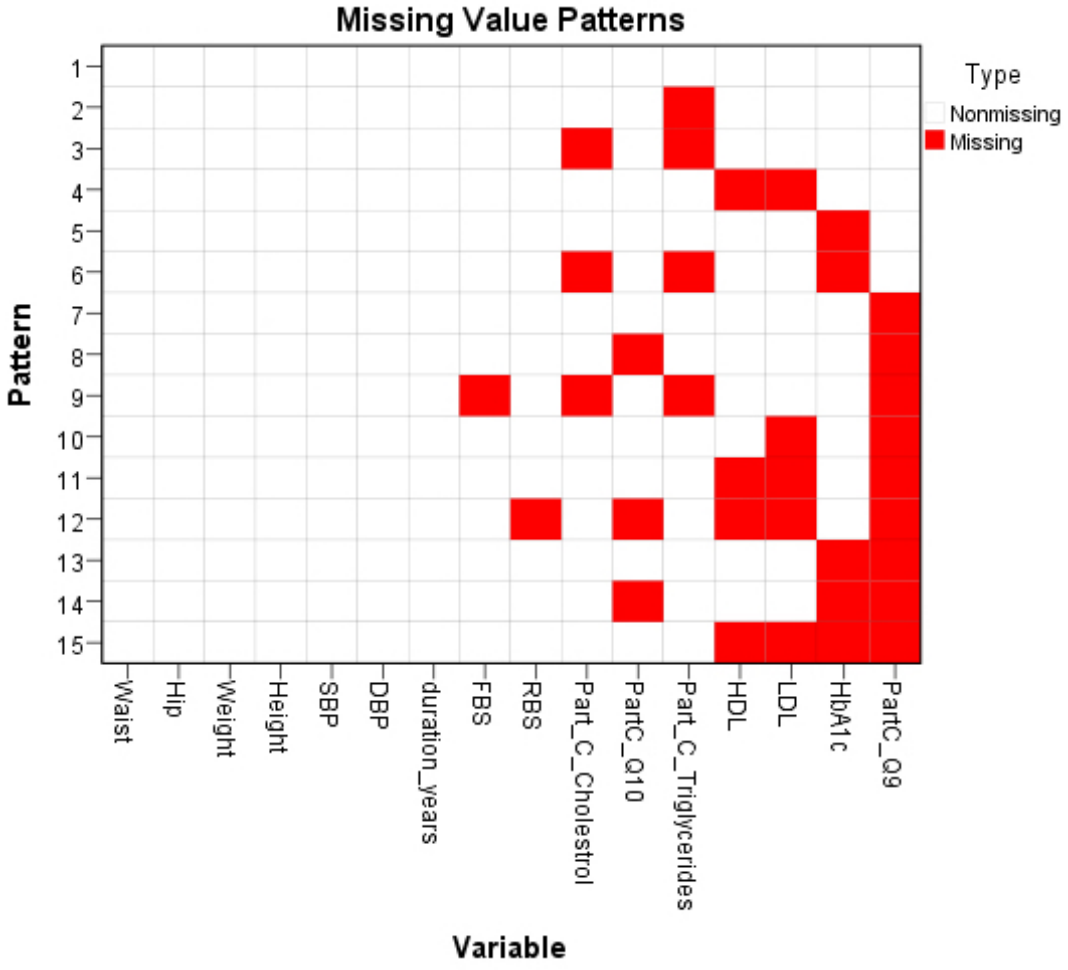

Figure 3: Missing values pattern showing data missing at random for 16 selected variables of all the patients(n=257)

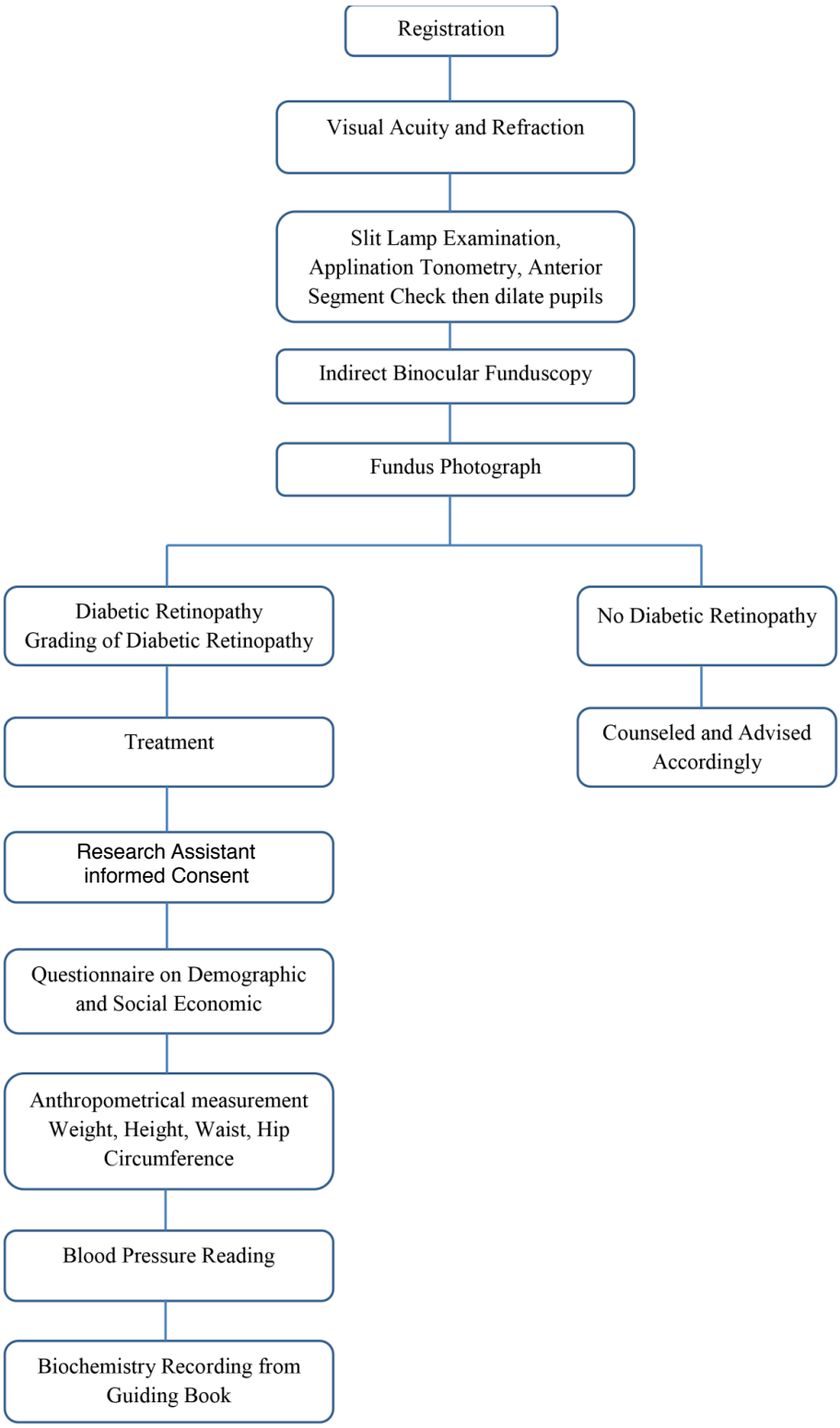

Figure 4: Flow chart of the procedure

3

RESULTS

3.1 DEMOGRAPHIC CHARACTERISTICS

Two hundred fifty seven patients aged thirty years to 80 years who attended out patient ophthalmic clinic at BIRDEM hospital agreed to participate in this study. Table 4 shows the demographic characteristics of the study participants by the type of retinopathy. There were more males (57%) than females (43%) and the majority of the participants were married (88%). DR distribution by gender is presented in Figure 6, where it is shown that the proportion of males with all forms of DR was higher than females. The proportions of the participants with NPDR, CSME and PDR were 36%, 43% and 21% respectively and presented in Figure 5

The distribution of participants by education status was as follows; 7% were illiterate, 30% had $\leq$ 5 years of primary education, 33% had 10 years of education, 12% had 12 years of education, 14% graduated with a Bachelors' degree, 3% were holders of Master degree and only 1% of the participants were Doctors. The majority of participants in all forms of retinopathy resided in the rural areas and semi urban (town) areas (72% NPDR, 72% CSME and 65% PDR) . DR was common among patients in the age group 50 -59 years. All types of diabetic retinopathy were common among those who earned less than 25000 taka. The majority of the respondents were non-smokers (87%). 88% of the patients with PDR were non-smokers compared to 12% who were smokers.

The descriptive analysis shown in Table 4 revealed that there were no significant differences in gender, marital status, education, type of residence, age groups, household income and smoking status and different types of retinopathy (P-values > 0.05).

The distributions of the primary and secondary outcomes by gender are presented in Table 5. There were no significant differences that were observed between the proportion of females and males with any form of DR, VI and ST. However, the analysis showed that the proportion of obese females was significantly higher than the proportion of obese males (P = 0.01). Abnormal WC and HDL were more prevalent among females than males (P < 0.01). The proportion of SBP among males was higher than females (P< 0.01)

Table 4: Demographic characteristics of the 257 participants attended to out patient clinic at BIRDEM hospital by DR

	Types of Retinopathy				
Demographic Factors	**NPDR**	**CSME**	**PDR**	**Total**	**P-value**
	n (%)	n (%)	n (%)	n (%)	
n (%)	92 (36)	110 (43)	55 (21)	257	0.47
Gender:–number (%)					
Female	41 (44)	43 (41)	26 (45)	110 (43)	0.86
Male	53 (56)	62 (59)	32 (55)	147 (57)	
Marital status–number (%)					
Married	87 (93)	91 (87)	47 (81)	225 (88)	0.11
Unmarried	0 (0)	2 (2)	1 (2)	3 (1)	0.42
Widowed	7 (7)	12 (11)	10 (17)	29 (11)	0.19
Education: – number (%)					
Illiterate	7 (7)	6(6)	6(10)	19(7)	0.56
Primary ($\leq$ 5 years of education)	24 (26)	34(32)	18(31)	76(30)	0.58
10 years of education	30 (32)	31(30)	24(41)	85(33)	0.30
12 years of education	13(14)	13(12)	5(9)	31(12)	0.41
Bachelor	16(17)	16(15)	4(7)	36(14)	0.23
Master	3(3)	4(4)	1(2)	8(3)	0.76
Doctorate	1(1)	1(1)	0(0)	2(1)	0.74
Type of residence: – number (%)					
Urban	26(28)	29(28)	20(35)	75(29)	0.19
Rural & Semi-urban (Town)	68(72)	76(72)	38(65)	182(71)	0.19
Age groups (years): –number (%)					
30 - 39	6(6)	7(7)	0(0)	13(5)	0.14
40 – 49	17(18)	14(13)	8(14)	39(15)	0.61
50 – 59	36(38)	44(42)	22(38)	102(40)	0.83
60 – 69	21(22)	32(30)	20(34)	73(28)	0.23
70+	14(15)	8(8)	8(14)	30(12)	0.24
Household income (Taka): – number (%)					
< 25000	56(60.9)	70(63.6)	33(60.0)	159(61.9)	0.88
$\geq$ 25000	36(39.1)	40(36.4)	22(40.0)	98(38.1)	0.87
Smoking status: – number (%)					
Smoker	14(15)	13(12)	7(12)	34(13)	0.84
Non-smoker	80(85)	92(88)	51(88)	223(87)	

Table 5: Distribution of primary and secondary outcomes of 257 patients who attended to outpatient clinic at BIRDEM hospital by gender

	Female	Male	Total	P-value*
n (%)	110(43)	147(57)	257(100)	0.03
DR				
NPDR	41 (37.3)	51(34.7)	92 (35.8)	0.4
CSME	44 (40.0)	66(44.9)	110 (42.8)	0.31
PDR	25 (22.7)	30(20.4)	55 (21.4)	0.42
Visual Impairment				
Normal ≥6118	43 (39.1)	69 (46.9)	112 (43.6)	0.21
Moderate 6118 – 6160	51 (46.4)	64(43.5)	115 (44.7)	0.38
Severe≤6160	16 (14.5)	14 (9.5)	30 (11.7)	0.34
STR				
YES	69 (62.7)	96 (65.3)	165 (64.2)	0.37
No	41 (37.3)	51 (34.7)	92 (35.8)	0.4
BMI				
Normal+Under weight ≤22.9	18(17.2)	41(28.7)	59(23.8)	0.17
Over weight 23–24.9	15(14.3)	34(23.8)	49(19.8)	0.23
Obese≥25	72 (68.6)	68 (47.6)	140 (56.5)	0.01
WHR				
≥ 0.8 Female,≥ 0.9 Male	110(100.0)	140 (95.2)	250 (97.3)	-
<0.8 Female, < 0.9 Male	0(0.0)	7(4.8)	7(2.7)	-
Duration of diabetes				
≤10 years	40 (36.4)	49 (33.3)	89 (34.6)	0.38
> 10 years	70 (63.6)	98 (66.7)	168 (65.4)	0.34
HDL				
<50 Female ,<40 Male	93 (85.3)	75 (52.8)	168 (66.8)	< 0.01
≥ 50 Female,≥ 40 Male	16(14.7)	67(47.2)	83(33.1)	0.01
LDL				
>100	48(44.0)	64(45.4)	125(50.0)	0.44
≤100	61(56.0)	77(54.6)	125(50.0)	0.43
HbA1c				
>9	34(58.6)	39(49.4)	73(53.3)	0.22
≤9	24(41.4)	40(50.6)	64(46.7)	0.24
SBP (Means±SD)	124.27±13.42	130.80±14.58	128.01±14.4	<0.01
DBP(Means±SD)	79.61±8.61	80.90±8.61	80.45±8.44	0.22

* P-values based on test of proportions between females and males.

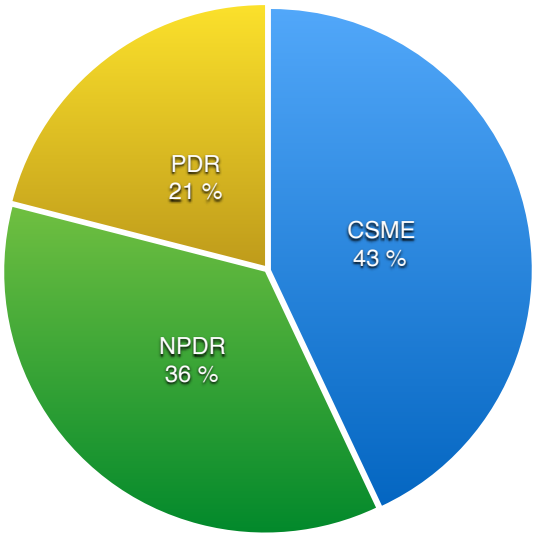

Figure 5: Distribution of types of Retinopathy among type 2 DM who attended out patient clinic at BIRDEM hospital

3.2 AGE AND TYPES OF RETINOPATHY

Table 6 shows comparisons of the mean ages at presentation, mean durations of DM and the mean ages at diagnosis for patients with NPDR, CSME and PDR. The average age at presentation for patients with CSME (55.7 years) was slightly lower compared to patients with PDR (57.1 years) and NPDR (58.7years). However, the analysis showed that these mean differences were not significantly different (P = 0.12).

The analysis also showed that the mean duration of DM was not statistically different between patients with the three types of retinopathy (P = 0.46). Although the analysis showed that the mean age at diagnosis was not statistically significant (P = 0.07), patients with NPDR were slightly older (44.5years) compared to patients with CSME (40.6 years) and PDR (43.5 years). 61.5 % of the participants had a late onset of DM compared to 38.5% who had an early onset of DM.

3.3 MEAN COMPARISON OF BLOOD PARAMETERS BY TYPE OF RETINOPATHY

Table 7 shows the means of the different blood parameters and their 95% CI in patients with different types of retinopathy. The Table also shows the P-values obtained from ANOVA, which tests the differences in mean values of the blood parameters for the different types of DR. Using the Least Significant Difference (LSD) test (for the post-hoc analysis) in ANOVA, patients with CSME had a higher mean cholesterol level compared to patients with NPDR (P = 0.04).

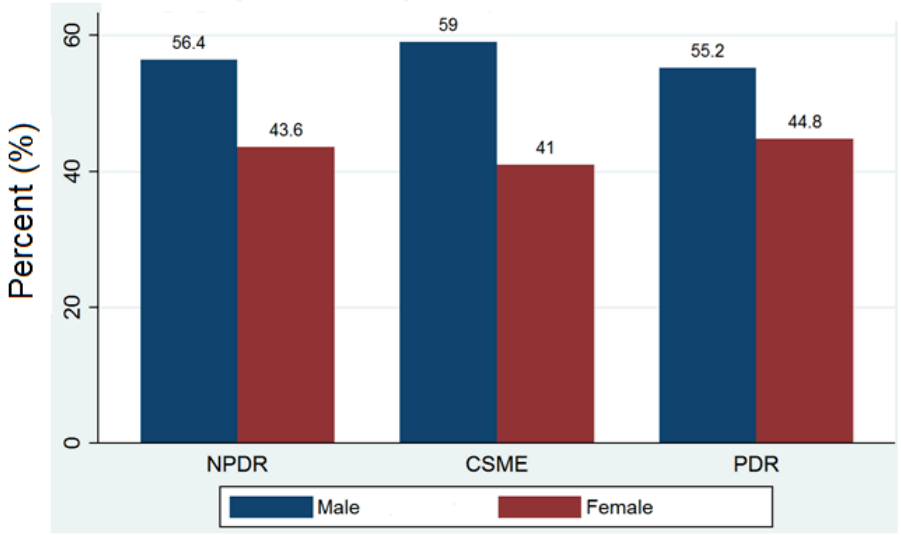

Figure 6: Distribution of types of Diabetic Retinopathy(%) among type 2 DM who attended out patient clinic at BIRDEM hospital by Gender

However, the analysis failed to show significant differences in mean values of the other blood parameters for the different types of DR (P-values > 0.05).

3.4 RELATIONSHIP BETWEEN LDL, HDL, CHOLESTEROL AND TG

Partial correlation coefficients (after controlling for the type of retinopathy) between the lipid profiles LDL, HDL, cholesterol and TG are presented in Figure 7. A moderate relationship (r = 0.51) using Pearson correlation was found between cholesterol and TG. Weak relationships were found between LDL and HDL, between LDL and cholesterol, between HDL and cholesterol, between triglycerides and LDL and also between triglycerides and HDL.

3.5 CORRELATION COEFFICIENTS, DIFFERENCES IN PROPORTIONS AND ASSOCIATIONS OF CLINICAL MEASURES BY GENDER

A strong positive relationship (r = 0.9) was found between the hip and waist in females whereas a moderate positive relationship (r = 0.57) was found between weight and hip in males as shown in Figure 8.

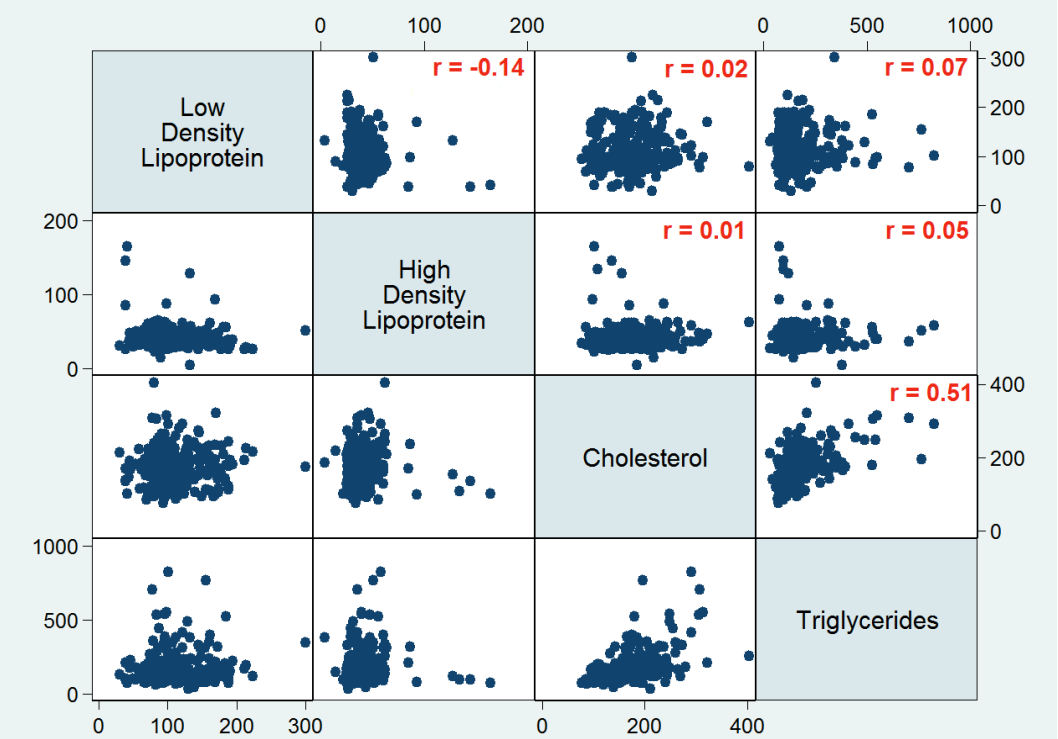

Figure 7: Correlation coefficients between LDL, HDL, Cholesterol and TG after Controlling for the Type of Retinopathy

Figure 8: Relationship between weight, waist and hip after controlling for DR by gender

Table 6: Detailed comparisons between patients with early onset and late onset DM presented with different stage of DR of the patients who attended to outpatient clinic at BIRDEM hospital

Age at Presentation					
	N (%)	NPDR	CSME	PDR	P-value*
	257	92	110	55	
Mean ± SD	57.1± 10.2	58.7 ± 9.9	55.7 ± 10.8	57.1± 8.9	0.12
Min-Max	30 - 80	30- 79	30 - 80	40- 79	
30-39	13 (5.1)	2 (2.2)	5 (4.5)	6 (10.9)	
40-49	39 (15.2)	14 (15.2)	13 (11.8)	12 (21.8)	
50-59	102 (39.7)	38 (41.3)	49 (44.5)	15 (27.3)	
60-69	73(28.4)	27 (29.3)	28 (25.5)	18 (32.7)	
>70	30 (11.7)	11 (12.0)	15 (13.6)	4 (7.3)	
Duration of DM (Years)					
Means ±SD	14.4 ± 7.2	14.2 ± 7.4	15.0 ± 7.5	13.7 ± 5.8	0.46
Min-Max	0.50 - 45	0.50 - 44	0.50- 45	4.0- 30	
< 5 Years	16 (6.2)	4(4.3)	8 (7.3)	4 (7.3)	
5–10	73 (28.4)	30 (32.6)	27 (24.5)	16 (29.1)	
> 10 Years	168 (65.4)	58 (63.0)	75 (68.2)	35 (63.6)	
Age at Diagnosis with DM (Years)					
Mean ±SD	42.6 ± 12.2	44.5 ± 12.7	40.6 ± 12.2	43.5 ± 11.2	0.07
Min-Max	19 - 75	20 - 71	20-75	19- 68	
Early onset DM < 40 Years	99 (38.5)	29 (31.5)	53(48.2)	17 (30.9)	
Late onset DM ≤40 Years	158 (61.5)	63 (68.5)	57(51.8)	38 (69.1)	

* P-values obtained from the analysis of variance (ANOVA).

Table 8 shows differences in proportions of clinical parameters between males and females and also the p-values for the associations between gender and clinical parameters using a chi-square test. On a p-value of 0.04, the proportion of males with abnormal waist hip ratio (54.1%) was significantly higher than the proportion of females (42.8%). However, differences in proportions for other clinical parameters were not statistically significant. P-values from the chi-square tests show that gender was significantly associated with BMI (P=0.007), waist circumference (P=0.001) and WHR (P=0.012) but not with WHtR (P=0.09).

Table 7: Mean differences in blood parameters by type of retinopathy using ANOVA

	Type of Retinopathy			
	NPDR	CSME	PDR	
Blood parameter	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	P-value
FBS	10.1 (8.3, 11.9)	9.0 (8.4, 9.7)	9.4 (8.4, 10.4)	0.44
RBS	11.8 (11.09, 12.6)	14.3 (12.3, 16.4)	12.6 (11.5, 13.8)	0.07
LDL	106.6 (98.8, 114.4)	116.3 (108.5, 124.2)	108.0 (97.6, 118.4)	0.18
HDL	39.7 (36.4, 42.9)	40.1 (37.6, 42.6)	45.7 (38.8, 52.6)	0.09
HbA1c	14.8 (3.1, 26.4)	8.8 (8.2, 9.5)	9.4 (8.5, 10.3)	0.36
Urea	34.5 (29.5, 39.5)	37.7 (29.2, 46.3)	31.9 (26.0, 37.7)	0.54
Creatinine	1.2 (1.0, 1.3)	3.3 (-0.6, 7.2)	1.8 (0.3, 3.2)	0.54
Triglycerides	162.6 (142.4, 182.8)	185.9 (161.7, 210.1)	170.6 (140.9, 200.4)	0.34
Cholesterol	167.2 (157.4, 177.0)	185.1 (174.3, 196.0)	171.3 (159.2, 183.5)	0.04

Table 8: Tests for differences in proportions of clinical measures by gender and the associations between gender and clinical measures using a chi-square test.

Clinical measures	**Male**	**Female**	**Total**	**P-value for differences in gender proportions**	**Chi-square[**] P-value**
Mass Index (BMI)					0.007
Under weight <18.5 +	6(2.3)	1 (0.4)	7 (2.7)	0.45	0.014
Normal from 18.9–22.9					
Over weight 23-24.9	34 (13.2)	18 (7.0)	52 (20.2)		
Obese≥25	69 (26.8)	73 (28.4)	142 (55.3)		
Waist circumference (WC)					
Normal	68 (26.5)	7 (2.7)	75 (29.2)	0.08	0.001
Abnormal[a]	79 (30.7)	103 (40.1)	182(70.8)	0.10	
Waist Hip Ratio (WHR)					
Normal	8 (3.1)	0 (0)	8 (3.1)	-	
Abnormal[b]	139 (54.1)	110 (42.8)	249 (96.9)	0.04	0.012
Waist Height Ratio (WHtR)					
Normal	15 (5.8)	2 (0.8)	17 (6.6)	0.38	0.09
Abnormal (> 0.5)	132 (51.4)	108(42.0)	240 (93.4)	0.07	

[a] ≤90 cm for males and ≤80 cm for Females.
[b] ≤0.90 for males and ≤0.80 for Females.
[**] Chi-square P-values for the associations between gender and the clinical parameters.

3.5.1 *Factors associated with DR*

Model results

Model results from the ordered logistic regression are presented in Table 9. The univariate analysis showed that SBP, residence (rural/ urban), BMI (over-weight) and LDL were significantly associated PDR development ($P < 0.05$). Model 1 is based on variables with $P < 0.2$ from the univariate analysis plus clinically relevant variables, which include age, duration of diabetes and gender. On the other hand, Model 2 is based on variables with $P < 0.05$ from the univariate analysis plus clinically relevant variables. The analysis showed that the risk for developing PDR versus NPDR and CSME combined was 2% high for each unit increase in SBP ($P = 0.01$). From the results in Model 2, the risk of PDR versus NPDR and CSME combined was 73% high in females compared to males. Participants who lived in the urban areas had a significantly higher risk of developing PDR than their rural counterparts (based on results from both Model 1 and 2).

A surprising result was that being over-weight seemed to offer a protective effect of developing PDR in this population. The analysis showed that the risk for developing PDR was 55% lower (based on Model 1 results), and 54% lower (based on Model 2 results) among the overweight participants compared to normal/ underweight participants. The results for obese participants were not statistically significant

3.6 VISUAL IMPAIRMENT (VI)

3.6.1 *Visual Acuity (VA) distribution based on the better eye*

Visual acuity measurements for the study participants are shown in Figure 9 The majority of the patients (44.7%) had moderate VA in the best eye (6/18-6/60). There were only 30 patients (11.7%) who had severe VA in the best eye ($\leq$6/60), whereas 43.6% had normal VA in both eye ($\geq$6/18)

3.6.2 *Distribution of VA in both eyes by gender*

The distribution of VA based on the best eye by gender is shown in Figure 10 The proportion of females with severe VA of the better eye (53.3%) was higher than the proportion of males

Table 9: Proportional Odds ratio and their 95% CI obtained from ordered logistic regression models for DR

	Univariate analysis Crude POR		Model 1 [1] Adjusted POR		Model 2 [2] Adjusted POR	
Explanatory variables	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Age	1.00 (0.98, 1.03)	0.87	1.01 (0.98, 1.03)	0.53	1.01 (0.98, 1.03)	0.52
Duration in years	1.01 (0.98, 1.04)	0.62	1.01 (0.97, 1.05)	0.72	1.01 (0.97, 1.05)	0.69
SBP	1.02 (1.00, 1.04)	0.02	1.02 (1.01, 1.04)	0.01	1.02 (1.01, 1.04)	0.01
DBP	1.02 (0.99, 1.05)	0.11				
Ref gender: Males						
Females	1.43 (0.89, 2.29)	0.14	1.66 (0.96, 2.89)	0.07	1.73 (1.02, 2.93)	0.04
Ref Residence: Semi-urban/ Rural						
Urban	2.13 (1.27, 3.57)	< 0.01	1.80 (1.05, 3.11)	0.03	1.79 (1.04, 3.08)	0.04
Ref SES : <25000 TBD						
≥ 25000 TBD	1.06 (0.65, 1.71)	0.82				
Ref BMI: ≤ 22.9 (Normal + underweight)						
23.0 – 24.9 (Overweight)	0.42 (0.21, 0.87)	0.02	0.45 (0.21, 0.96)	0.04	0.46 (0.22, 0.96)	0.04
≥ 25 (Obese)	1.02 (0.58, 1.78)	0.95	0.99 (0.54, 1.83)	0.98	1.01 (0.54, 1.86)	0.98
Ref HDL: (≥ 50 Females; ≥ 40 Males)						
(< 50 Females; < 40 Males)	1.47 (0.89, 2.42)	0.13	1.15 (0.66, 2.01)	0.62		
Ref LDL: ≤ 100						
> 100	1.69 (1.05, 2.72)	0.03	1.52 (0.92, 2.52)	0.1	1.55 (0.94, 2.55)	0.09
Ref HbA1c: <9						
≥9	0.99 (0.52, 1.89)	0.99				
Ref WHR: (< 0.8 Females; < 0.9 Males)						
(≥ 0.8 Females; ≥ 0.9 Males)	0.40 (0.10, 1.54)	0.18	0.30 (0.07, 1.24)	1	0.30 (0.73, 1.23)	1
Insulin ref: Non-users						
Users	1.61 (0.77, 3.36)	0.21				

[1] Model 1 is based on variables with P < 0.2 from the univariate analysis plus clinically relevant variables.
[2] Model 2 is based on variables with P < 0.05 from the univariate analysis plus clinically relevant variables.

Table 10: Distribution of Visual Acuity based on the best eye among patients who attented BIRDEM hospital

Visual acuity	n	Proportion (95% CI)
Normal	112	43.6 (34.4-52.7)
Moderate	115	44.7 (35.6- 53.8)
Severe	30	11.7 (0.2-23)

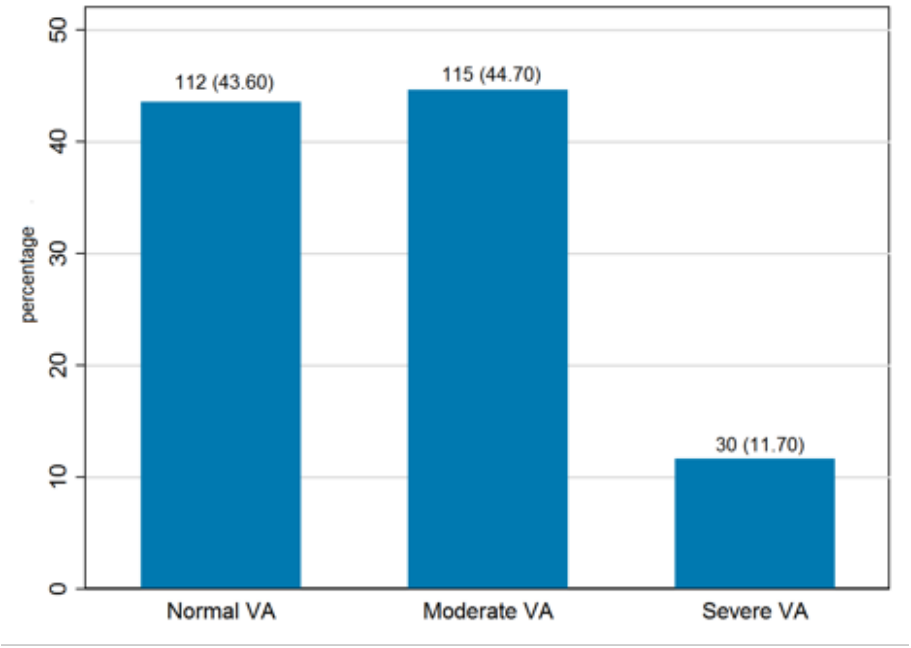

Figure 9: Distribution of visual acuity based on the best eye for patient with type 2 DM who attended out patient clinic at BIRDEM hospital

with severe VA of the better eye (46.7%).Whereas the proportion of males with normal VA and moderate VA of the better eye was higher than females.

3.6.3 *VA distribution based on the best eye by type of DR*

The distribution of severity of VA based on the better eye by DR is shown in Table 10. Most of the participants with CSME (46.7) and with PDR (43.3%) had severe VA. However, severe VA of the better eye was also observed in 3 study participants with NPDR.

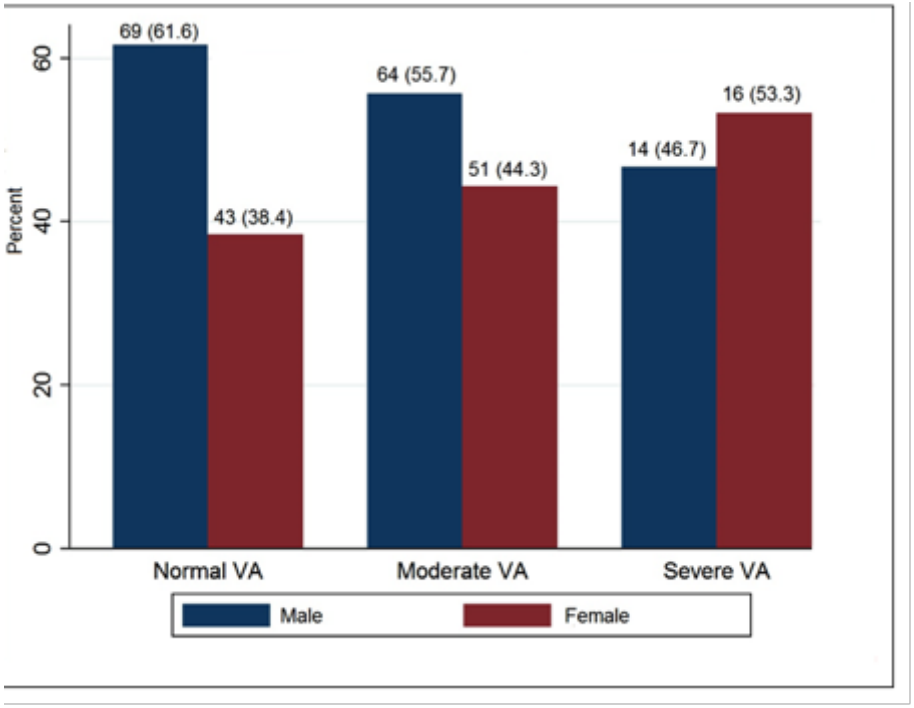

Figure 10: Distribution of VA based on the best eye (%) among patients with type 2 DM who attended out patient clinic at BIRDEM hospital by Gender

3.6.4 *Factors associated with VI*

Model results from the ordered logistic regression are presented in Table 12, Model 1 is based on variables with P < 0.2 from the univariate analysis plus clinically relevant variables, which include age, duration of diabetes and gender. On the other hand, Model 2 is based on variables with P < 0.05 from the univariate analysis plus clinically relevant variables. The risk of developing severe Visual Impairment versus (normal and moderate) was 80% higher for residents compared to semi urban and rural residents combined.

The analysis showed that the risk for developing severe Visual Impairment versus normal and moderate combined was 2% high for each unit increase in SBP (P = 0.02).

3.6.5 *Sight threatening by gender*

The proportion of ST for both females and males in different age groups and at different levels of duration are presented in Figures 11 and 12 respectively. Between the age groups 30-39 and 50-59, the proportion of males with ST conditions was lower than the proportion of females. However, from the age of 60, the proportion of males is higher than the proportion of females

Table 11: Distribution of VA based on the better eyes by type of DR for patients with type 2 DM who attended out patient clinic at BIRDEM hospital

	Normal $\geq$ 6/18	Moderate 6/18-6/60	Severe $\leq$ 6/60	Total
n (%)	112 (43.6)	115 (44.7)	30 (11.7)	257 (100)
Retinopathy Type (n)				
NPDR (92)	59 (52.2)	30 (26.1)	3 (10.0)	92 (35.8)
CSME (110)	44 (39.3)	52 (45.2)	14 (46.7)	110 (42.8)
PDR (55)	9 (8.0)	33 (28.7)	13 (43.3)	55 (21.4)
P-value[1]	0.097	0.04	0.12	0.16
P-value[2]	0.01	0.41	0.14	0.03

[1] P-value test the proportion between NPDR and CSME
[2] P-value test the proportion between NPDR and PDR

with ST conditions. On the other hand, the proportion of males with ST conditions was higher if they had diabetes for < 20 years. The proportion of females (23.2%) with diabetes duration of 20 - 25 years and at a risk of developing ST was higher than the proportion of males (13.5%) as shown in Figure 12.

3.6.6 *Median duration before ST*

In Table 13, the median time for the development of ST condition for females after they were diagnosed with diabetes is 17 years compared to 15 years for males. The Kaplan-Meier plot in Figure 13 shows that there were 147 male patients and 110 female patients who were at risk of developing ST conditions. After 10 years, 116 of the 147 males had not developed ST giving a survival rate of 79% compared to 77% (85/110). After 30 years, all females would have developed ST compared to 45 years for males. However, a test for the difference in time (years) leading to development of ST between females and males using the log rank test showed that there were no significant differences (P = 0.53). By considering the slopes of the Nelson-Aalen estimator, we see that the hazard rate for females is larger than the hazard rate for males after 20 years.

Table 14 shows the hazard rates for factors associated with ST from the univariate Cox regression model. For each year increase in age, the risk for developing ST condition increased by 5%. There were no other significant predictors of ST that were found in this study.

Table 12: Crude and adjusted proportional odds ratio (POR) and their 95% CI from the ordinal logistic regression models for VI

	Crude POR		Adjusted POR [1]		Adjusted POR [2]	
Explanatory variables	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Age	1.00 (0.98, 1.02)	0.88	1.01 (0.98, 1.03)	0.53	1.01 (0.98, 1.03)	0.53
Ref gender: Males						
Females	1.43 (0.89, 2.29)	0.14	1.66 (0.96, 2.87)	0.07	1.61 (0.96, 2.70)	0.07
Duration:	1.01 (0.98, 1.04)	0.62	1.01 (0.97, 1.05)	0.72	1.01 (0.97, 1.05)	0.71
HDL ref ≥50 F ≥ 40 M						
< 50 F, < 40 M	1.47 (0.89, 2.42)	0.13	1.15 (0.66, 2.01)	0.72		
Ref HbA1c ref < 9						
Abnormal (≥9)	0.99 (0.52, 1.89)	0.99				
WC ref <0.5						
Abnormal (≥0.5)	1.07 (0.65, 1.79)	0.79				
WHR ref <0.8 F, <0.9 M						
Abnormal(≥0.8F, ≥0.9M)	0.40 (0.10,1.5)	0.18	0.30 (0.07, 1.25)	0.1		
Ref BMI: ≤22.9 + Underweight+Normal						
Overweight 23-24.9	0.42 (0.21, 0.87)	0.02	0.45 (0.21, 0.96)	0.04	0.42 (0.20, 0.89)	0.02
Obese≥25	1.02 (0.58, 1.78)	0.95	0.99 (0.54, 1.83)	0.98	0.93 (0.51, 1.69)	0.8
LDL ref: Normal < 100						
Abnormal >100	1.69 (1.05, 2.71)	0.03	1.52 (0.92, 2.52)	0.1	1.58 (0.97, 2.60)	0.07
FBS ref: <7						
Abnormal (≥7)	1.11 (0.66, 1.86)	0.69				
Insulin ref: Non-users						
Users	1.61 (0.77, 3.36)	0.21				
SBP	1.02 (1.00, 1.04)	0.02	1.02 (1.01, 1.04)	0.01	1.02 (1.01, 1.04)	0.02
DBP	1.02 (0.99, 1.05)	0.11				
Ref Residence: Semi-urban/ Rural						
urban	2.13 (1.27, 3.57)	< 0.01	1.80 (1.05, 3.11)	0.03	1.80 (1.05, 3.10)	0.03
Ref SES						
<25000 TBD						
≥25000 TBD	1.06 (0.65,1.71)	0.82				

[1] Model 1 is based on variables with P < 0.2 from the univariate analysis plus clinically relevant variables.
[2] Model 2 is based on variables with P < 0.05 from the univariate analysis plus clinically relevant variables.

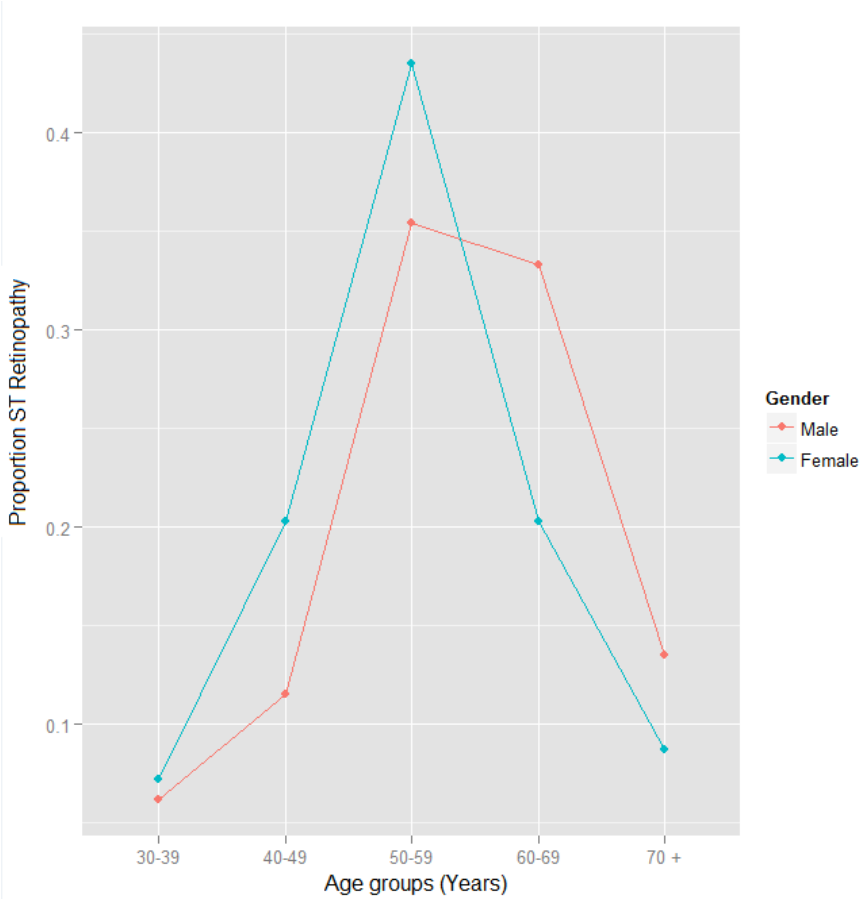

Figure 11: Proportion of STR for males and females in different age groups of 257 patients who attended to out patient clinic at BIRDEM hospital

Table 13: Median time and their 95% CI for the onset of STR by gender of 257 patients who attended to outpatient clinic at BIRDEM hospital

		95% CI	
Gender	Median survival time	Lower	Upper
Female	17.0	15.0	19.0
Male	15.0	13.5	16.5

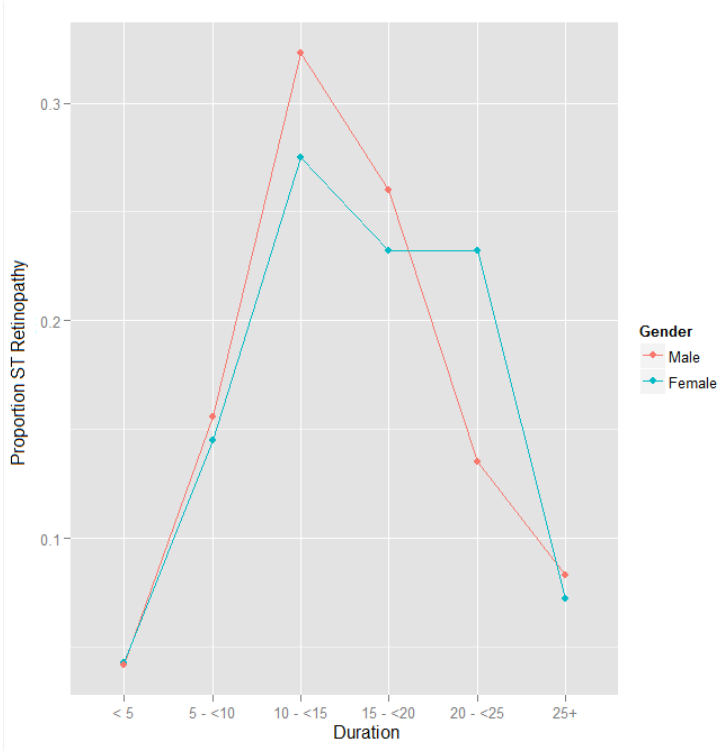

Figure 12: Proportion of STR for males and females at different levels of duration for type 2 DM of 257 patients who attended to outpatient clinic at BIRDEM hospital.

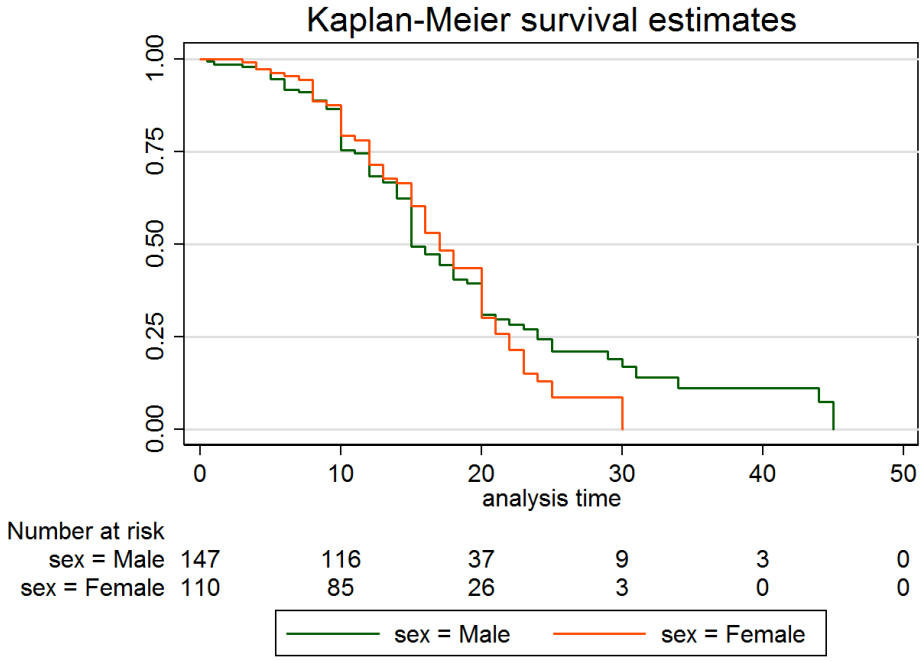

Figure 13: Kaplan-Meier estimates for the proportion of males and females developing STR conditions of 257 patients who attended to outpatient clinic at BIRDEM hospital

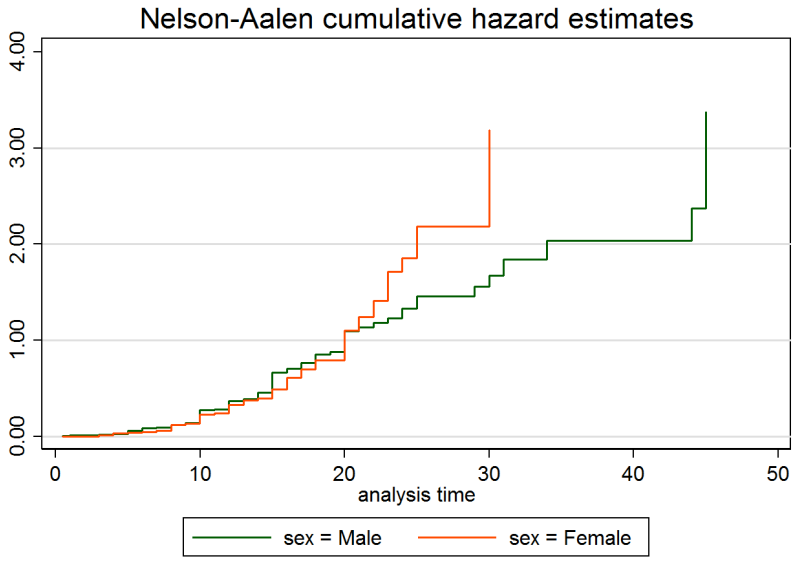

Figure 14: Cumulative hazard for the instantaneous risk of developing STR of 257 patients who attended to outpatient clinic at BIRDEM hospital

Table 15 shows the hazards rate for factors associated with ST from the multivariate Cox regression model. For each year increase in age, the risk for developing ST condition significantly increased by 5%. For each unit increase in LDL and HDL, the risk of ST significantly increases by 1%.

Table 14: Univariate Cox regression model for the risk of developing STR of 257 patients who attended to outpatient clinic at BIRDEM hospital

Covariate	**Hazard rate**	**95% CI**	**P-value**
Covariate	Hazard rate	95% CI	P-value
Age	1.05	(1.03, 1.06)	< 0.01*
Gender (Ref:Male)			
Female	1.10	(0.80,1.50)	0.55
BMI	0.97	(0.93, 1.01)	0.17
HDL	1	(0.99, 1.01)	0.24
LDL	1	(0.99, 1.01)	0.16
HbA1c	0.95	(0.95, 1.03)	0.6
Cholesterol	1	(0.99, 1.01)	0.08
WHR	0.53	(0.25, 1.15)	0.11
WC	0.82	(0.59, 1.13)	0.23
FBS	1	(0.97, 1.03)	0.77
Diabetes medication (Ref: Insulin)			
Diet	0.33	(0.05, 2.33)	0.26
Oral hyperglycemia	1.52	(0.90, 2.57)	0.12
Insulin + oral	0.85	(0.58, 1.24)	0.39
HTN: Antihypertensive medications	0.75	(0.54, 1.04)	0.08

Table 15: Multivariate Cox regression model for the risk of developing STR of 257 patients who attended to outpatient clinic at BIRDEM hospital

Covariate	Hazard rate	95% CI	P-value
Age	1.05	(1.04, 1.07)	< 0.01*
Gender (Ref :Male)			
Female	1.02	(0.73, 1.39)	0.97
HDL	1.01	(1.00, 1.02)	0.05
LDL	1.01	1.00, 1.01)	0.02
FBS	1	(0.96,1.03)	0.84

4

DISCUSSION

4.1 FINDINGS

In this study, an assessment of sight threatening and visual impairment among patients diagnosed with DR was done. The study also attempted to look at the differences in characteristics of DR types and severity among diagnosed type 2 DM.

The prevalence of STR was higher among patients with CSME (43%) than that with PDR (21%).The prevalence of sight-threatening PDR was found to be higher in a study conducted by Memom et.al in Pakistan than this study at 31%. Their estimate of sight-threatening CSME (47%) was also higher than this study, which gives the estimate of 43% (43). However, lower estimates of sight-threatening PDR were found in studies of prevalence of retinopathy by Agrawal et.al in India of 14.6% and Kayani et. al in Pakistan of 11.8%. This shows that the prevalence of sight-threatening PDR varies from population to population even among the Asian countries (44; 45).

In this study, the overall proportion of patients with STR was estimated to be 64.2%. This was comparable to a study done by Momen et al. in Pakistan, which found it to be 64%. However, the estimates of STR prevalence were found to be lower in other previous studies. For instance, in a study conducted by Shah and Kanaya on diabetes and associated complications in the South Asian population, the prevalence of STR was found to be 16% (46; 45). A much lower prevalence of STR of 10% among Asians was reported in the DRIVE UK study (47). To the best of our knowledge, studies of STR (CSME and PDR) are yet to be reported among diabetic patients of Bangladesh.

Gender differences for ST conditions were not observed in this study. This is in agreement with the findings of Younis et al. on the incidence of STR in patients with type 2 DM (36). The authors did not identify significant relation between sex and incidence of STR. However, the findings here and those of Younis et al. are in contrast with the findings in the UK Prospective Diabetic study, where men had significantly higher rates of progression than women (48). A possible reason could be that the two studies looked at STR conditions from two different settings, UK and Bangladesh.

In this study, the multivariate Cox regression model showed that HDL, and LDL, were associated for the risk of developing STR. The same results were found by Miljanovic et al in a prospective study of serum lipids and risks of diabetic macular edema in type 1 diabetes (49). However, these findings are in contrast with Beijing Eye study among Chinese population that found at there is no association between dyslipidemia and STR (34). Other studies done by Rahman et al., Kardonouri et al.,and Sinav et al found that only HDL increased the risk of STR (50; 51; 52). Conversely, Klein et al in a study on the relationship in people with diabetes in cardiovascular disease found that progressive retinopathy was not associated with (53).On the other hand some other researchers such as van Leiden et al, found LDL increased the risk of STR in the Hoorn study (54), and Sach dev and Sahni found LDL affecting STD among the north Indian population (55).

The multi Cox regression model showed also that for each year increase in age, the risk for development STR will increase by 5%. The same result was obtained by Pardhan et al on Impact of age and duration on sight threatening retinopathy in south Asians and Caucasians attending a diabetic clinic of each year increased by age, the risk of STR increased by 8% (56).

One other major finding in this current study is that the median time to STR diagnosis was estimated at 17 years in females compared to 15 years in males. A study in Bangladesh by Ahmed et al. on the incidence of DR showed that the mean time until development of DR in men was 9.8 years while in females it was 9.6 years. The finding in this study is in partial agreement with the findings of Palmberg et.al on the diabetic retinopathy who reported that more than 60% of type 2 DM patients will have evidence of DR 15–20 years after being diagnosed (57). On the other hand, this finding is higher than the findings of Klein et.al, Jones et al and Nathan et al., regardless of gender, Klein et al. reported the incidence of CSME 9 to 10 years after diabetes was diagnosed (58). The same result was published in a study assessing type 2 DM patients by Jones et al who found that only 1% proliferative sight threatening developed after 9 years of diabetes follow up (59). Nathan et al reported on following diabetic patients that the prevalence of retinopathy increases fourfold after duration of 10 years with diabetic without mentioning the grade of progression of DR (60). This difference could be due to the difficulty to recognize accurately the exact onset of type 2 DM because patients may have an asymptomatic period of undiagnosed DM before being diagnosed.

The overall proportion of patients with visual impairment was 56.4% in this study, which was higher than the findings from studies by Javadi et al., and Damato et al. The prevalence of visual impairment in a study of diabetic retinopathy in Tehran province by Javadi et al. was found to be 2.7%, while in a study on sight-threatening DR in Fiji by Damato et al the prevalence of visual impairment was reported to be 9.4% (61; 62) .This difference could be explained by the fact that the developed countries have more screening and health awareness programs for

early detection of DM complications, which is in contrast to the developing countries, where the patients are more likely to get diagnosed on being symptomatic. However, the prevalence of visual impairment among the general Bangladeshi population in the national survey was 13.8% and DR was not the main cause of blindness or visual loss (63).

This study found a prevalence of severe VI of 11.7% which is in regard with the findings of a study in Pakistan by Khan et al, where the prevalence of severe visual impairment was 15%(64).However a much lower prevalence of severe VI was reported in other studies, including, a study on the prevalence of sight threatening retinopathy and visual impairment caused by diabetes in Malawi, Burgess et al found that the prevalence of severe VI was 1.6% (65).

Few studies have reported VI and systolic blood pressure .In this study systolic blood pressure is statistically significant associated with VI based on the better eye, with 2% high for each unit increase in SBP (P-value= 0.02) .A similar result was obtained by Chong in a study of socio-demographic lifestyle and medical risk factors for visual impairment in an urban Asian population in Singapore (66). Limited studies have evaluated BMI and VI; interestingly, high BMI (over weight) is inversely associated with VI in this study. This finding is comparable to a study done by Chong in Singapore Malay eye study (66).The risk of developing severe VI versus moderate and normal was 80% higher for urban residents compared to semi-urban and rural residents combined. This result can reflect that the eye screening for the diabetic patients is low even among the urban residents.

No relation was found between VI and education, or marital status or income .These results are in contrary with other studies such as Los Angeles Latino eye study (51), and Singapore Malay eye study (50) which found increased VI with lower education, and among widowed, and unemployed .But, was in agreement with Liu et al, that found no relationship with marital status ,or income with VI among Taiwanese population (67).Although women showed a trend to be more visually impaired than men, the result was not statistically significant in this study.

In regards to the development of DR, several risk indicators were found in the ordered logistic regression to be associated with DR .The analysis showed that each unit increase in SBP, the development of PDR versus NPDR and CSME combined was increased by 2%. This significant trend was consistent with Raymond et al findings on high prevalence of retinopathy in diabetic patients of South Asian ethnicity compared with white Europeans in the community, of high systolic blood pressure was associated with DR in patients from south Asians (68). Moreover the UK prospective Diabetes study (UKPDS) revealed that reduction in DR incidence is associated by blood pressure control (48).

The analysis also demonstrates that female gender increased the risk of PDR verses NPDR and CSME combined. This result is in consistent with a study by Sparrow et al on the prevalence

of diabetic retinopathy and maculopathy and their risk factors in the non-insulin-treated diabetic patients of an English town, that found female sex, higher BP are risk factors for DR, and DR severity (69).Although other previous studies contradicts this result, and found male gender increase the development of any DR such as Rani et al., Pradeepa et al (70; 58).

One other risk indicator found in this study that Urban residents had a higher risk of developing PDR than the residents in semi urban and rural combined .One of the explanation is that the rapid epidemiological transition combined with changes in the dietary pattern was approved for increasing the diabetes prevalence and diabetes complications prevalence among the urban population than rural (71).

A surprising result was that BMI particularly over weight inversely associated with the development of PDR versus NPDR, CSME combined. However, this result contradicts another study which found high BMI indicate a high risk for developing DR (37).Although; BMI was not mentioned as a risk factor for DR in the CURES, or in the Finnish study (73, 74)(72; 49).

Another surprising results of this study were that HBA1c level was not associated with STR or with DR. The associations of HbA1c on STR and DR are well documented in literature. For example, Kim et al. in a study on development and progression of DR and associated risk factors showed that the significant predictor that can lead to the development of DR was abnormal HbA1c (73). Akhter et al. showed that HbAc1 was a significant risk indicator for the occurrence of retinopathy in a study on the prevalence and associated risk indicators of retinopathy in rural Bangladeshi population with and without diabetes (37). One of the explanations for this discrepancy is that the different settings used in different studies such as the selected group in this study was already diabetic patients and on treatment.

4.2 METHODOLOGICAL REFLECTIONS, CONCLUSION AND RECOMMENDATIONS

4.2.1 *Statistical analysis*

This is a cross sectional study in which we assessed different factors that affect types of DR, and STR, and VI among diagnosed DR. It is important to be aware that multiple factors may have influenced on the dependent factors DR, STR, VI.

One variable may have significant relationship with the dependent variable, but this association may have been due to the influence of third variables, called a confounder factor. To control for the confounding factors, We have used multi variate logistic regression analyses with PDR and ST as the dependent factors .We have used adjusted proportional odds ratio with DR and

with VI .However, we cannot exclude the possibility that there might be uncontrolled factors that were not included in the study and analysis.

4.2.2 *Sample size*

We have used a formula for estimating the sample size based on prevalence and it required at least 252 persons, and we managed to include 257 patients.

4.2.3 *Selection Bias*

Our sample was collected from one hospital, BIRDEM, but BIRDEM is the main diabetic hospital where all the diabetic patients in Dhaka and all over the country come for diagnosis and follow up.This also can be the reason for high prevalence of STR, and VI because the sample was collected from a tertiary hospital.

4.2.4 *Validity*

There are two types of validity; the internal validity and the external validity. The internal validity in my study refers to the tests performed to the patients. The biological specimen that analyzed at BIRDEM laboratory, considered as one of the best laboratories in Bangladesh. We used the Fundus photography for diagnosis of DR which considers the golden standard tools where the sensitivity and specificity are high .The photography was done in the hospital and performed by well trained staff. Anthropometric measurements and the simple clinical examination were performed following the WHO standards procedures .We used questionnaire that was translated from English to Bengali and from Bengali to English to make sure that it did not lose the meaning during the translation process. A small pilot was also done before carrying out the study. The external validity is the ability to generalize the results to the general population. Since we have used cross sectional study that included hospital outpatient diabetic, and since BIRDEM hospital controls the diabetic care in Dhaka, therefore our sample most likely reflects the diabetic outpatient hospital population in Dhaka. The external validity is the ability to generalize the results to the general population. Since we have used cross sectional study that included hospital outpatient diabetic, and since BIRDEM hospital controls the diabetic care in Dhaka, therefore our sample most likely reflects the diabetic outpatient hospital population in Dhaka.

4.3 CONCLUSION

Even though this study is relatively small and findings should be articulated with caution, the data regarding DR from the south Asian population, where the type 2 diabetes is likely to increase substantially in the near future .Therefore, the data is vital to develop appropriate preventive measures and improve the quality of life for the diabetic patients and also, decreasing the economic burden on the patients and the community.

In summary, it can be concluded that the overall STR prevalence in this population was 64.2% , and prevalence of VI was 56.4%. The risk for occurrence of STR is related to increasing age, and LDL, HDL abnormality levels. One of the risks for increasing VI and PDR was high SBP. Despite of the importance of STR investigation, and visual impairment detection in order to provide preventive measures and quality of care, we lack simple, accurate and readily reproducible method to measure the rate and the extent of ST in low income countries and visual impairment among diabetic patients. Moreover the modifiable factors such as LDL,HDL ,and SBP can be controlled to be at normal levels, and so the risk will be reduced or diminished. These risk patients should be identified in time and receive improved care through proper education, screening and follow up, so the risk of impairment will be diminished and furthermore the cost will be reduced upon the individual and the society at large.

4.4 RECOMMENDATIONS

In addition to the useful experience and observation gained during the field work, the data presented in this study produce several questions and issues that demand further evaluation.

In a country like Bangladesh with limited resources, high density population with increasing life expectancy and increasing the prevalence of diabetes and it's comorbidity. The burden on the health system will rise dramatically, so the need for community mobilisation for the prevention of diabetic modifiable risk factors becomes urgent.

Health awareness and health promotion become necessary. The community needs to know and needs to give attention to the importance of diabetic prevention in general and its complication in order to improve the quality of their life.

.

APPENDIX

A

REQUEST FOR PARTICIPATION IN A RESEARCH PROJECT

"Factors associated with Retinopathy in early diagnosed and late diagnosed type 2 diabetes in Bangladesh"

BACKGROUND AND PURPOSE:

Diabetic Retinopathy is a condition that leads to damage of the retina of the eye due to persistent high blood glucose levels in people with poorly controlled diabetes. However, retinopathy can also occur in patients with high blood pressure. Some studies has been done all over the world to investigate the factors that associated with retinopathy and they found that certain life style factors and physical characteristics like weight, high cholesterol can be associated with retinopathy. Other studies found that there are some controlled factors that can help to diagnose diabetic retinopathy early such as the duration of diabetes, time of diagnosis. Therefore the purpose of this research is to study extensively the factors that are associated with Retinopathy in early diagnosed and late diagnosed type 2 diabetes patients.

WHAT DOES THE STUDY ENTAIL?

If you have been diagnosed with retinopathy after the fundus photography, and you consent to participate in this research you will be registered and enrolled. You will be subjected to an interview which you will be asked some questions about your life style, medical history, and diet, etc. You will be subjected to blood tests and urine tests for which you will have to come to (BIRDEM) Lab early morning with overnight fasting of 12 hours. The expenses for the travel will be provided to you.

POTENTIAL ADVANTAGES AND DISADVANTAGES:

The advantage of participating in this study is that participants will be subjected to various blood tests which can be diagnose undiagnosed abnormalities like deranged serum cholesterol levels, protein urea. Withdrawing blood can be uncomfortable. This has no adverse effect. Blood will be taken by professional staff.

All the information provided by the participants will be kept entirely confidential and all possible measures will be carried out to protect and secure this information. All the blood and urine samples will be used for the above study only and after reading the results all the samples will be destroyed. This study will not provide any intervention to the participants, and so provision of any insurance is not necessary. All the participants in this study will be informed of their blood and urine result and will be informed of the research result.

CONSENT FOR PARTICIPATION IN THE STUDY

I am willing to participate in the study titled "Factors associated with Retinopathy in early diagnosed and late diagnosed type 2 diabetes in Bangladesh", and I have been given complete information about this study.

Signature and Date (Participant)

Signature and Date (Principal Investigator)

B

QUESTIONNAIRE

Case ID:

Retinopathy type:

☐ NPDR

☐ CSME

☐ PDR

PART A

SOCIO-DEMOGRAPHICS

S.NO	VARIABLES	RESPONSES	CODE
1	Age	..... in years 1.30-39 years 2. 40-49 years 3. 50-59 years 4. 60-69 years 5. 70 years or above	
2	Gender	1. Male 2. Female	
3	Marital Status	1. Married 2. Unmarried 3. Separated 4. Divorced 5. Widowed	
4	Education	0 ..... No of Years 1. Illiterate 2. Primary (less than or equal to 5 years of education 3. Matriculation(10 Class) 4. Intermediate(12 Class) 5. Graduation (16 Class) 6. Masters 7. Doctorate 8. Post Doc	
5	Household Income	..... BDT	

LIFE STYLE

S.NO	VARIABLES	RESPONSES	Skip Pattern	CODE
6	Do you smoke?	1. Yes 2. No 3. Former smoker	If NO, proceed to 9	
7	If Yes, What do You smoke?	1. Cigarette 2. Pipe 3. Cigar 4. Other (please specify		
8	How frequent do you smoke?	1. Daily 2. Occasionally (once or twice a week) 3. Only in parties 4. Others (please specify)		

MEDICAL & DRUG HISTORY

S.NO	VARIABLES	RESPONSES	Skip Pattern	CODE
9	Do you have any of these conditions? (multiple choices can be checked)	1. Diabetes Mellitus type 2. Hypertention 3. CKD 4. Cardiac 5.Others (Please specify)		
10	Have you ever had Myocardial Infarction (heart attack) or have you ever suffered from Angina Pectoris?	1. Yes 2. No		
11	If you have Diabetes Mellitus, then for how long have you suffered from it?	0 . . . . . in Years 1. Past six months 2. Past one year 3. 1-2 years 4. 2-3 years 5. 3-4 years 6. 4-5 years 7. More than 5 years		

MEDICAL & DRUG HISTORY contd.

S.NO	VARIABLES	RESPONSES	Skip Pattern	CODE
12	How often do you check your blood sugar levels?	1. Daily 2. Once or twice a weak 3. Once in two weeks 4. Monthly 5. Only when I go to my doctor 6. Others (please specify)		
13	Are you on any kind of medication?	1. Yes 2. No	If NO, proceed to 16	
14	If Yes, What medications do you take? (multiple choices can be checked)	1. Antihypertensive 2. Oral Hypoglycemic 3. Insulin 4. Steroids 5. Anti hyper lipidemia 6. Anti Coagulation 7.Others		
15	For how long have you been on these medications?	0. . . . . In years 1. Past six months or less 2. Past year 3. 1-2 years 4. 2-3 years 5. 3-4 years 6. 4-5 years 7. More than 5 years		

☐ early diagnosed type 2 diabetes

☐ late diagnosed type 2 diabetes

FAMILY HISTORY

S.NO	VARIABLES	RESPONSES	Skip Pattern	CODE
16	Do you have a family history of any on these conditions? (multiple choices can be checked)	1. Diabetes Mellitus type 1 2. Diabetes Mellitus type 2 3. Hypertension 4. Cardiac 5. No family history		
17	Has anyone in your family ever suffered from Retinopathy?	1. Yes 2. No 3. Don't Know		
18	Has anyone in your family suffered from blindness?	1. Yes 2. No 3. Don't Know		
19	How long have you feel with eye problems?			
20	-VA Right Eye -VA Left Eye			

PART B

PHYSICAL EXAMINATION

S.NO	Variable	Value
1	Height	
2	Weight	
3	Waist Circumference	
4	Hip Circumference	
5	Systolic Blood Pressure	
6	Diastolic Blood Pressure	

PART C

LAB INVESTIGATIONS

S.NO	Investigation	Value
1	Fasting Blood Glucose	
2	Random Blood Glucose	
3	Fasting Insulin Levels	
4	Low Density Lipoprotein	
5	High Density Lipoprotein	
6	Triglycerides	
7	Total Cholesterol	
8	HbA1c	
9	Urea	
10	Creatinine	

C

ETHICAL CLEARANCE

বাংলাদেশ ডায়াবেটিক সমিতি
DIABETIC ASSOCIATION OF BANGLADESH

Memo No. BADAS-ERC/EC/14/00195 Date: December 6, 2014

Rula Hadad
M phil Student
Department of International Community Health
University of Oslo

Subject: Ethical Clearance

The Ethical Review Committee (ERC) of the Diabetic Association of Bangladesh (BADAS) has approved your protocol on "Factors Associated with Retinopathy in Patients with late Diagnosed and early Diagnosed Type -2 Diabetes in Bangladeshi Population."

K.M.S. Aziz

(Dr. KMS Aziz)
Chairman
Ethical Review Committee

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Adviser:	Telephone:	Our date:	Our reference:
REC South East	Harsha Gajjar Mikkelsen	22845513	03.11.2015	2014/857 REK sør-øst B
			Your date: 01.10.2015	

Akhtar Hussain
University of Oslo

2014/857 Diabetic retionopathy in Bangladesh and its risk factors

Institution responsible for research: University of Oslo
Chief Investigator: Akhtar Hussain

We are writing in reference to the Project Amendment Application Form dated the 1st of October 2015 for the abovementioned Research Project. Secretariat REC South East has assessed the amendment form on delegated authority pursuant to section 11 of the Health Research Act 2008.

Chief Investigator's description of the Research Project
"Diabetes Mellitus (DM) is associated with micro vascular complications .Diabetic Retinopathy (DR) is the most common specific complication of type 2 diabetes, and is one of the main leading cause of visual loss in individuals aged 20-64 years old .Type 2 Diabetes is characterized by Asymptomatic phase between the actual onset of diabetic hyperglycemia and clinical diagnosis. This phase has been estimated to last between 4-7 years and as a result 30-50% of type 2 diabetes remaining undiagnosed .As a consequence of untreated hyperglycemia, high prevalence of retinopathy in new diagnosed diabetic patients was found.Only in western
countries studies conducted among early diagnosed diabetes and fundus photography was used. Such a data is scarce in south Asia in general and particularly in Bangladesh. The aim of the study is to explore extensively the association between DR and a variety of risk factors for retinopathy among early diagnosed and late diagnosed diabetic Type 2"

Amendment
The Chief Investigator has applied for the following amendment to the Research Project:

1. It was previously stated in the Research Protocol that blood and urine samples would be collected from the participants. The Chief Investigator now wishes to obtain this information from the patients' journals, as these values are already noted in their journal.

Review
The Committee has no objections to the proposed amendment.

Decision
The Committee approves the application for Amendment to the Research Project, in accordance with section 11 of The Health Research Act 2008.

The project is approved on the condition that it is conducted as described on the Project Amendment Application Form.

Appeals process
The decision of the Committee may be appealed to the National Committee for Research Ethics in Norway. The appeal will need to be sent to the Regional Committee for Research Ethics, Section B, South East Norway, The deadline for appeal is three weeks from the date on which you receive this letter.

With kind regards,

Knut W. Ruyter
Divisional Director for the Regional Committee for Medical &
Health Research Ethics of South East Norway

Harsha Gajjar Mikkelsen
Senior Executive Officer

CC:
- *Management of Administration, University of Oslo*
- *Faculty of Medicine, University of Oslo*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Administrator:	Telephone:	Our date:	Our ref.:
REK sør-øst	Jakob Elster	22845514	01.07.2014	2014/857 REK sør-øst B
			Your date:	Your ref.:
			13.05.2014	

Akhtar Hussain

University of Oslo

2014/857 Diabetic retionopathy in Bangladesh and its risk factors

Institution responsible for Research: University of Oslo
Project Manager: Akhtar Hussain

We are writing in reference to your application for approval for the above mentioned Research Project. The Committee reviewed the application during its meeting on the 11th of June 2014. The project was assessed in accordance to the Health Research Act (2008) § 10, and Norwegian Research Ethics Act (2008) § 4.

Project description
The background for the project is that Diabetes Mellitus (DM) is associated with micro vascular complications. Diabetic Retinopathy (DR) is the most common specific complication of type 2 diabetes, and is one of the main leading causes of visual loss in individuals aged 20-64 years old. Type 2 Diabetes is characterized by an asymptomatic phase between the actual onset of diabetic hyperglycemia and clinical diagnosis. This phase has been estimated to last between 4-7 years and as a result 30-50% of type 2 diabetes remaining undiagnosed. As a consequence of untreated hyperglycemia, a high prevalence of retinopathy in new diagnosed diabetic patients has been found.

The aim of the study is to explore extensively the association between DR and a variety of risk factors for retinopathy among early diagnosed and late diagnosed diabetic Type 2 patients in the Bangladeshi population. 250 patients with early diagnosed or late diagnosed diabetes type 2 and diagnosed with retinopathy will be recruited to the study. Information regarding their socio-demographic characteristics, life style, medical and drug history, and family medical history will be obtained. A medical examination will be performed, including blood and urine samples. Participation is based on informed consent. If the patient is illiterate or unable to sign, so that written consent cannot be given, a thumb impression will be taken.

The Committee's Assessment
The committee has no ethical objections to the project.

The committee presupposes that the project is approved by the local ethical body in Bangladesh.

The Committee's Decision
The project is approved, in accordance with the Norwegian Health Research Act § 9 and § 33.

The approval is given on condition that the project is conducted as described in the application and the protocol.

The approval is valid until 15.01.2015. The data must be stored as de-identified data, i.e. with identifying information kept separate from the other data. For purposes of documentation, the data shall be kept until 15.01.2022 and deleted or anonymised after this date.

The data must be stored in accordance with the norms of data protection in *personopplysningsforskriften* chapter 2, and the guide "*Personvern og informasjonssikkerhet I forskningsprosjekter innenfor helse- og omsorgssektoren*", published by the Norwegian Directorate of Health.

If the project manager wants to make substantial changes to the objective, method, schedule or organisation of the research project, an application must be submitted to the Regional Committee for Medical and Health Research Ethics. The project manager must submit a final report to the Regional Committee for Medical and Health Research Ethics when the research project is finished.

The decision of the Committee may be appealed to the National Committee for Research Ethics in Norway. The appeal will need to be sent to the Regional Committee for Research Ethics in Norway, South-East B. The deadline for appeals is three weeks from the date on which you receive this letter.

Med vennlig hilsen

Grete Dyb
Chair of the Regional Committee for Medical
& Health Research Ethics of South East Norway,
Section B

Jakob Elster
Senior Adviser

CC: *Head of administration, University of Oslo*

BIBLIOGRAPHY

[1] Kollias AN, Ulbig MW. Diabetic retinopathy: early diagnosis and effective treatment. Deutsches Arzteblatt International. 2010;107(5):75.

[2] Kanski JJ, Bowling B. Klinische Ophthalmologie. Urban & Fischer in Elsevier; 2012.

[3] CIA. The world factbook: Country profiles; 2015. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/xx.html [cited 15 November 2015].

[4] Weiss A, Andersen A, Depiante G, Bittencourt M, Sankei P. The Bangladesh Development Report. 2013;.

[5] Demographic B. Health Survey 2011. Dhaka: National Institute of Population Research and Training (NIPORT); 2013;.

[6] Bangladesh population and housing census 2011. Bangladesh Bureau of Statistics; 2012.

[7] Kurshed AAM, Rana MM, Khan S, Azad TA, Begum J, Bhuyan MAH. Dietary intake, physical activities and nutritional status of adolescent girls in an urban population of Bangladesh. Ibrahim Medical College Journal. 2010;4(2):78–82.

[8] UNICEF, et al. Child and mother nutrition survey in Bangladesh, 2005. Dhaka (Bangladesh): UNICEF. 2007;.

[9] Ahmed T, Mahfuz M, Ireen S, Ahmed AS, Rahman S, Islam MM, et al. Nutrition of children and women in Bangladesh: trends and directions for the future. Journal of health, population, and nutrition. 2012;30(1):1.

[10] Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. The lancet. 2008;371(9608):243–260.

[11] Islam A BT. The Health System in Bangladesh: Challenges and opportunities. American Journal of Health Research. 2014;2:366–374.

[12] Statistical Yearbook 2011-2012. Diabetic Association Bangladesh; 2012. Available from: http://www.dab-bd.org/images/statistical_Report_2012.pdf [cited 15 November 2015].

[13] Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. Jama. 2002;287(19):2519–2527.

[14] Mitra AR, Janjua I. Diabetes in south Asians: etiology and the complexities of care. UBC Medical Journal. 2010;2(1).

[15] Lewis CP, Newell JN. Patients' perspectives of care for type 2 diabetes in Bangladesh-a qualitative study. BMC public health. 2014;14(1):737.

[16] Statistics from Diabetic Association of Bangladesh (DAB); 2015. Available from: http://www.diabetes-bd.org.

[17] Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bulletin of the world health organization. 2004;82(11):844–851.

[18] Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Archives of ophthalmology. 1984;102(4):520–526.

[19] Davidov E, Breitscheidel L, Clouth J, Reips M, Happich M. Diabetic retinopathy and health-related quality of life. Graefe's Archive for Clinical and Experimental Ophthalmology. 2009;247(2):267–272.

[20] Marshall SM, Flyvbjerg A. Clinical review-Prevention and early detection of vascular complications of diabetes. BMJ-British Medical Journal-International Edition. 2006;333(7566):475–480.

[21] Diabetes. Fact Sheet no. 312.2012. World Health Organization Media Centre; 2012. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/ [cited 15 November 2015].

[22] Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. Survey of ophthalmology. 2012;57(4):347–370.

[23] Shah CA, et al. Diabetic retinopathy: A comprehensive review. Indian journal of medical sciences. 2008;62(12):500.

[24] Group ETDRSR, et al. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. Ophthalmology. 1991;98(5):786–806.

[25] Group DRSR, et al. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. Ophthalmology. 1981;88(7):583–600.

[26] Group ETDRSR, et al. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology. 1991;98(5):741–756.

[27] Kollias AN, Ulbig MW. Diabetic retinopathy: early diagnosis and effective treatment. Deutsches Arzteblatt International. 2010;107(5):75.

[28] Garg S, Davis RM. Diabetic retinopathy screening update. Clinical Diabetes. 2009;27(4):140.

[29] Mather HM, Keen H. The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans. BMJ. 1985;291(6502):1081–1084.

[30] Namperumalsamy P, Kim R, Vignesh T, Nithya N, Royes J, Gijo T, et al. Prevalence and risk factors for diabetic retinopathy: a population-based assessment from Theni District, south India. British Journal of Ophthalmology. 2009;93(4):429–434.

[31] Raman R, Rani PK, Rachepalle SR, Gnanamoorthy P, Uthra S, Kumaramanickavel G, et al. Prevalence of diabetic retinopathy in India: sankara nethralaya diabetic retinopathy epidemiology and molecular genetics study report 2. Ophthalmology. 2009;116(2):311–318.

[32] Mahar P, Awan MZ, Manzar N, Memon MS. Prevalence of type-II diabetes mellitus and diabetic retinopathy: the Gaddap study. J Coll Physicians Surg Pak. 2010;20(8):528–532.

[33] Shaikh A, Shaikh F, Shaikh ZA, Ahmed J. Prevalence of diabetic retinopathy and influence factors among newly diagnosed diabetics in rural and urban areas of Pakistan: Data analysis from the Pakistan National Blindness & Visual Impairment Survey 2003. Pak J Med Sci. 2008;24:774–779.

[34] Xie XW, Xu L, Wang YX, Jonas JB. Prevalence and associated factors of diabetic retinopathy. The Beijing Eye Study 2006. Graefe's Archive for Clinical and Experimental Ophthalmology. 2008;246(11):1519–1526.

[35] Wang FH, Liang YB, Zhang F, Wang JJ, Wei WB, Tao QS, et al. Prevalence of diabetic retinopathy in rural China: the Handan Eye Study. Ophthalmology. 2009;116(3):461–467.

[36] Akhter A, Fatema K, Ahmed SF, Afroz A, Ali L, Hussain A. Prevalence and associated risk indicators of retinopathy in a rural Bangladeshi population with and without diabetes. Ophthalmic epidemiology. 2013;20(4):220–227.

[37] Younis N, Broadbent DM, Vora JP, Harding SP. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. The Lancet. 2003;361(9353):195–200.

[38] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical chemistry. 1972;18(6):499–502.

[39] Ferris FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. American journal of ophthalmology. 1982;94(1):91–96.

[40] Deitel M. Overweight and obesity worldwide now estimated to involve 1.7 billion people. Obesity surgery. 2003;13(3):329–330.

[41] Alberti KGM, Zimmet P, Shaw J, Group IETFC, et al. The metabolic syndrome—a new worldwide definition. The Lancet. 2005;366(9491):1059–1062.

[42] Consultation W. Definition, diagnosis and classification of diabetes mellitus and its complications. Part; 1999.

[43] VII.H54 Blindness and low vision. In: International statistical classification of diseases and related health problems. 10th ed. World Health Organization; 2003. .

[44] Agrawal R, Ranka M, Beniwal R, Gothwal S, Jain G, Kochar D, et al. Prevalence of diabetic retinopathy in type 2 diabetes in relation to risk factors: Hospital based study. Int J Diabetes Dev Ctries. 2003;23:16–9.

[45] Kayani H, Rehan N, Ullah N. Frequency of retinopathy among diabetics admitted in a teaching hospital of Lahore. J Ayub Med Coll Abbottabad. 2003;15(4):53–6.

[46] Shah A, Kanaya AM. Diabetes and associated complications in the South Asian population. Current cardiology reports. 2014;16(5):1–16.

[47] Sivaprasad S, Gupta B, Gulliford MC, Dodhia H, Mohamed M, Nagi D, et al. Ethnic variations in the prevalence of diabetic retinopathy in people with diabetes attending screening in the United Kingdom (DRIVE UK). 2012;.

[48] Stratton I, Kohner E, Aldington S, Turner R, Holman R, Manley S, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia. 2001;44(2):156–163.

[49] Miljanovic B, Glynn RJ, Nathan DM, Manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. Diabetes. 2004;53(11):2883–2892.

[50] Rahman MR, Arslan MI, Hoque MM, Mollah FH, Shermin S. Serum Lipids and Diabetic Retinopathy in Newly Diagnosed Type 2 Diabetic Subjects. Journal of Enam Medical College. 2012;1(2):63–66.

[51] Kordonouri O, Danne T, Hopfenmüller W, Enders I, Hövener G, Weber B. Lipid profiles and blood pressure: are they risk factors for the development of early background retinopathy and incipient nephropathy in children with insulin-dependent diabetes mellitus? Acta Paediatrica. 1996;85(1):43–48.

[52] Sinav S, Onelge M, Onelge S, Sinav B. Plasma lipids and lipoproteins in retinopathy of type I (insulin-dependent) diabetic patients. Annals of ophthalmology. 1993;25(2):64–66.

[53] Klein R, Marino EK, Kuller LH, Polak JF, Tracy RP, Gottdiener JS, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. British journal of ophthalmology. 2002;86(1):84–90.

[54] Van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, et al. Blood Pressure, Lipids, and Obesity Are Associated With Retinopathy The Hoorn Study. Diabetes care. 2002;25(8):1320–1325.

[55] Sachdev N, Sahni A, et al. Association of systemic risk factors with the severity of retinal hard exudates in a north Indian population with type 2 diabetes. Journal of postgraduate medicine. 2010;56(1):3.

[56] Pardhan S, Gilchrist J, Mahomed I. Impact of age and duration on sight–threatening retinopathy in South Asians and Caucasians attending a diabetic clinic. Eye. 2004;18(3):233–240.

[57] Palmberg P, Smith M, Waltman S, Krupin T, Singer P, Burgess D, et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. Ophthalmology. 1981;88(7):613–618.

[58] Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy XV: the long-term incidence of macular edema. Ophthalmology. 1995;102(1):7–16.

[59] Jones CD, Greenwood RH, Misra A, Bachmann MO. Incidence and progression of diabetic retinopathy during 17 years of a population-based screening program in England. Diabetes care. 2012;35(3):592–596.

[60] Nathan DM, Singer DE, Godine JE, Harrington CH, Perlmuter LC. Retinopathy in older Type II diabetics association with glucose control. Diabetes. 1986;35(7):797–801.

[61] Javadi MA, Katibeh M, Rafati N, Dehghan MH, Zayeri F, Yaseri M, et al. Prevalence of diabetic retinopathy in Tehran province: a population-based study. BMC ophthalmology. 2009;9(1):12.

[62] Damato EM, Murray N, Szetu J, Sikivou BT, Emma S, McGhee CN. Sight-threatening Diabetic Retinopathy at Presentation to Screening Services in Fiji. Ophthalmic epidemiology. 2014;21(5):318–326.

[63] Dineen B, Bourne R, Ali S, Huq DN, Johnson G. Prevalence and causes of blindness and visual impairment in Bangladeshi adults: results of the National Blindness and Low Vision Survey of Bangladesh. British Journal of Ophthalmology. 2003;87(7):820–828.

[64] Khan A. Age sex and duration relationship and prevalence of Diabetic retinopathy in Pakistani population. Pak J Ophthalmol. 1990;6:6–8.

[65] Burgess P, Allain T, García-Fiñana M, Beare N, Msukwa G, Harding S. High prevalence in Malawi of sight-threatening retinopathy and visual impairment caused by diabetes: identification of population-specific targets for intervention. Diabetic Medicine. 2014;31(12):1643–1650.

[66] Chong EW, Lamoureux EL, Jenkins MA, Aung T, Saw SM, Wong TY. Sociodemographic, lifestyle, and medical risk factors for visual impairment in an urban asian population: the singapore malay eye study. Archives of ophthalmology. 2009;127(12):1640–1647.

[67] Teuscher A, Schnell H, Wilson PW. Incidence of diabetic retinopathy and relationship to baseline plasma glucose and blood pressure. Diabetes Care. 1988;11(3):246–251.

[68] Raymond NT, Varadhan L, Reynold DR, Bush K, Sankaranarayanan S, Bellary S, et al. Higher prevalence of retinopathy in diabetic patients of South Asian ethnicity compared with White Europeans in the Community A cross-sectional study. Diabetes care. 2009;32(3):410–415.

[69] BIRCH MK, ROSENTHAL AR. The prevalence of diabetic retinopathy and maculopathy and their risk factors in the non-insulin-treated diabetic patients of an English town. Eye. 1993;7:158–163.

[70] Rani P, Raman R, Chandrakantan A, Pal S, Perumal G, Sharma T, et al. Risk factors for diabetic retinopathy in self-reported rural population with diabetes. Journal of postgraduate medicine. 2009;55(2):92.

[71] Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian journal of medical research. 2007;125(3):217.

[72] Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: the Chennai Urban Rural Epidemiology Study (CURES) eye study, I. Investigative ophthalmology & visual science. 2005;46(7):2328–2333.

[73] Kim YJ, Kim JG, Lee JY, Lee KS, Joe SG, Park JY, et al. Development and Progression of Diabetic Retinopathy and Associated Risk Factors in Korean Patients with Type 2 Diabetes: The Experience of a Tertiary Center. Journal of Korean medical science. 2014;29(12):1699–1705.


UNIVERSITAS OSLOENSIS
MDCCCXI