INCIDENCE OF DIABETIC RETINOPATHY: A 15 YEAR FOLLOW UP IN A HOSPITAL POPULATION (BANGLADESH)

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TO

MY BELOVED FATHER
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ABSTRACT

Objective: The study was designed to estimate the incidence and factors of diabetic retinopathy among Bangladeshi type 2 diabetic subjects.

Methods: A random sample of 977 diabetic patients were recruited in 2008 from amongst those who were first time diagnosed in 1993 in the outpatient department of the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM). From Patient Guide Books baseline data on clinical, anthropometric and biochemical parameters were collected and, at the time of the study, ie at the end of 15 year follow up blood glucose, lipid profile, HbA1c and serum creatinine were measured in addition to clinical and anthropometric features. A structured questionnaire was administered to collect dietary history and socio-demographic information. Diabetes was diagnosed following the WHO diagnostic criteria. Diabetic Retinopathy (DR) was diagnosed by retinal color photography and classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS). All patients were examined by an Ophthalmologist and were reconfirmed by a senior Ophthalmologist. Data were first compiled through a custom made software and imported into SPSS version 12.0. Appropriate formula was used to estimate stratified incidence rate per 1000 person-years and 95% confidence intervals. To reduce time the formula was put into SPSS 16.0 using syntax to perform the calculation. Student’s t test was performed to compare between Diabetic Retinopathy and No Diabetic Retinopathy. Univariate and multivariate generalized linear models were used to assess the associations of clinical, biochemical and anthropometric variables with retinopathy. The associations were presented in the form of relative risks (RRs) and 95% Confidence Intervals (CIs). When the univariate analyses showed significant relationship (p < 0.25) between exposure variables and retinopathy, then these exposure variables (risk factors) were further included into the multivariate analysis. A p-value less than 0.05 was considered to be statistically significant. All p-values presented are two tailed. The data were analyzed using a computer program Statistical Package for Social Science (SPSS) (Windows version 16.0).
Results: The incidence rates of DR (95% CI) were 23.54 (19.61-28.26), 17.52 (14.93-20.55) and 21.47 (18.86-24.44) per 1000 person-years at 5, 10 and 15 years respectively. The study showed a high incidence of DR at 5 years and relatively lower incidence at 10 years and an increased incidence at 15 years after diagnosis. Incidence of DR increased with increasing age, but this was more prominent in female subjects. Most of the moderate to severe NPDR cases were identified at 15 years after diagnosis.

Patients with retinopathy had worse glycemic control during three different time periods than patients without retinopathy (HbA1c 9.6±2.6 vs 7.7±2.3%, 9.9±2.1 vs 8.0±2.3% and 10.38±2.1 vs 7.27±1.5%, respectively; P<0.05). Glycaemic control, measured either by FBG or OGTT and HbA1C, was found to be the strongest risk factors for 5, 10 and 15 years of incidental cases of diabetic retinopathy controlling for potential confounding factors. It was also noted that age, area of residence, occupation, total cholesterol, triglycerides, the serum creatinine level and hypertension were significantly associated with the development of retinopathy in this study. Nevertheless multivariate model showed increasing age, FBG, 2 hr BG, A1C, TG and SBP were important independent risk factors for the development of DR. Measures of obesity like BMI and intake of nutrients were not found to be associated with the incidental cases of DR.

Conclusion: Bangladeshi type 2 diabetic subjects show a fairly high rate of DR and NPDR. The incidence increases with age with predominance in female and the severity of the condition increases with the duration of diabetes. Along with duration of diabetes glycemic control was the prime significant risk factor for the development of retinopathy in 15 year follow-ups. Other potential risk factors include elevated blood pressure, TG and the presence of nephropathy. A closer cooperation between the diabetologists and ophthalmologists is required to reduce the risk of complications and improve the quality of care.

Key words- Type 2 diabetes, Incidence, Diabetic retinopathy, Risk Factors.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ADA</td>
<td>American Diabetic Association</td>
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<tr>
<td>BDT</td>
<td>Bangladeshi Taka</td>
</tr>
<tr>
<td>BIRDEM</td>
<td>Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorder</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>BBS</td>
<td>Bangladesh Bureau of Statistics</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CURES</td>
<td>The Chennai Urban Rural Epidemiology Study Eye Study</td>
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<td>DAB</td>
<td>Diabetic Association of Bangladesh</td>
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<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
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<td>DM</td>
<td>Diabetes Mellitus</td>
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<tr>
<td>DCCT</td>
<td>The Diabetes Control and Complications Trial</td>
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<tr>
<td>DISS</td>
<td>Diabetes Incidence Study in Sweden</td>
</tr>
<tr>
<td>DR</td>
<td>Diabetic Retinopathy</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediamine Tetra-acetic Acid</td>
</tr>
<tr>
<td>FBG</td>
<td>Fasting Blood Glucose</td>
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<td>FP</td>
<td>Family Planning</td>
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<tr>
<td>gm</td>
<td>Gram</td>
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<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
<td>------------------------------------------------------</td>
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<tr>
<td>NHN</td>
<td>National Healthcare Network</td>
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<tr>
<td>OGGT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>OPD</td>
<td>Out patient Department</td>
</tr>
<tr>
<td>P</td>
<td>Probability</td>
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<td>PAL</td>
<td>Physical Activity Level</td>
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<tr>
<td>RR</td>
<td>Relative Risk</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Science</td>
</tr>
<tr>
<td>TC</td>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<tr>
<td>U.S.C</td>
<td>Union sub-centers</td>
</tr>
<tr>
<td>U.S.A</td>
<td>United State of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WESDR</td>
<td>The Wisconsin Epidemiologic Study of Diabetic Retinopathy</td>
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<tr>
<td>WHR</td>
<td>Waist to hip Ratio</td>
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<tr>
<td>Wt</td>
<td>Weight</td>
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Chapter 1

Introduction
1. Introduction
1.1 Country Profile: Bangladesh

Bangladesh is one of the most low-lying and densely populated country in the world. Almost 20 million of its people are extremely poor and vulnerable to natural disaster. It is striving to become a middle-income country with much reduced poverty (1). A brief overview of the country is given below:

1.1.1 Geography
Bangladesh, on the northern coast of the Bay of Bengal, is surrounded by India, with a small common border with Myanmar in the southeast. The country is low-lying riverine land traversed by the many branches and tributaries of the Ganges and Brahmaputra rivers. The country has an area of 144,000 square kilometres and extends 820 kilometres north to south and 600 kilometres east to west. Tropical monsoons and frequent floods and cyclones inflict heavy damage in the delta region (2).

1.1.2 History
Europeans began to set up trading posts in the area of Bangladesh in the 16th century; eventually the British came to dominate the region and it became part of British India. In 1947, West Pakistan and East Bengal (both primarily Muslim) separated from India (largely Hindu) and jointly became the new country of Pakistan. East Bengal became East Pakistan in 1955, but the awkward arrangement of a two-part country with its territorial units separated by 1,600 km left the Bengalis marginalized and dissatisfied. East Pakistan seceded from its union with West Pakistan in 1971 and was renamed Bangladesh and then Bangladesh achieved full independence in 1971 (3).

1.1.3 Population
According to the world fact book 2008 total population of Bangladesh is 150,448,339 and the density of population per square kilometre is 800. The annual growth rate of the population has come down to 2.05% and the rate of child mortality per 1000 has come down to 59.12. The sex ratio is 106 males for every 100 females and life expectancy at birth is 62.84 years. 98 percent of the people of Bangladesh are Bangalees. The major religion is Muslim with 80 percent of total population.
1.1.4 Education

Highest allocations for education in the national budgets during the nineties show that the government has attached top most priority to human resource development though education. In Human Development Report 2007/2008, the current literacy rate of Bangladesh is 47.5%. To promote literacy among women, free education for girls up to class ten, stipends for female students, food-for educational total literacy movement and nationwide integrated education are some of the major programs being the government in the education sector. In Bangladesh, the education system is divided into 4 levels--Primary (from grades 1 to 5), Secondary (from grades 6 to 10), Higher Secondary (from grades 11 to 12) and tertiary (graduate and above).

1.1.5 Economy

The economy has grown 5-6% over the past few years despite inefficient state-owned enterprises, delays in exploiting natural gas resources, insufficient power supplies, and slow implementation of economic reforms. Bangladesh remains a poor, overpopulated, and inefficiently-governed nation. Although more than half of GDP is generated through the service sector, nearly two-thirds of Bangladeshis are employed in the agriculture sector, with rice as the single-most-important product. Garment exports and remittances from Bangladeshis working overseas, mainly in the Middle East and East Asia, fuel economic growth (3).

1.1.6 Overall Health Status in Bangladesh

There has been substantial progress in disease prevention and control and a decline in childhood communicable diseases, new and old infectious diseases, such as malaria, tuberculosis and acquired immunodeficiency syndrome (AIDS) are important threats to health for the years ahead. Bangladesh has been experiencing an epidemiological transition from communicable diseases to non-communicable diseases. Non-communicable diseases are a heterogeneous group that includes major causes of death, such as heart diseases, diabetes and cancer, and disability, such as mental disorders. NCDs are important cause of disease burden, morbidity and mortality. At least 25% of the deaths in primary and secondary government health facilities are caused by these diseases. These are also on the rise in Bangladesh (4). Tertiary level hospital data
indicate that cardiovascular diseases have already appeared as one of the leading causes of mortality. The Health, Nutrition, Population Sector Programme (HNPS) has identified three NCDs-cancer, cardiovascular diseases and diabetes mellitus-as major public health problems (5). Presently, Bangladesh does not have a community-based public health program for NCDs. Only hospital-based information, although poor, is available (6).

1.1.7 Health care system in Bangladesh
The Ministry of Health and family Welfare (MOHFW) is responsible to ensure basic health care to the people of the country. Administratively, the country is divided into 6 divisions, 64 districts, 460 upazilas (sub-district) of which 397 are rural and remaining 63 are sadar (district town) and 4451 unions. Public sector health system is structured as primary, secondary and tertiary level health care (7).
Primary level health care is delivered through union sub-centers (U.S.C)/ Health and Family Welfare Center (H.F.W.C). The secondary level health care is provided through 100 bed district hospitals. These facilities provide specialist services in medicine, surgery, gynecology and obstetrics, eye, clinical pathology, blood transfusion and public health laboratory. Tertiary level health care is available at the medical college hospitals/post graduate, public health and medical institutes and other specialist hospitals at the National level where a much wide range of specialized as well as better laboratory facilities are available (8). Besides the public sector, private and NGOs (Non Governmental Organization) also play large roles in the Bangladesh health sector.

1.1.8 Nutrition situation in Bangladesh
1.1.8.1 Nutritional status
Children and women in Bangladesh suffer from high levels of malnutrition and micronutrient deficiencies such as low birth weight (LBW), under nutrition (underweight, stunting and wasting), vitamin A deficiency, iodine-deficiency disorders (IDD) and iron-deficiency anemia (IDA). At the same time, new health problems related to over-nutrition such as obesity are emerging. Despite considerable improvement in the national rural health status, the nutritional well-being of rural people continues to be neglected (9). Low birth weight is more common among adolescent mothers. Marriage at very young age has serious consequences for pregnancy, future survival, health, growth
and development. When combined with positive energy balance (adequate energy intake) in later life, LBW increases the risk of obesity, diabetes, high blood pressure and coronary heart disease (10, 11). Bangladesh has made significant progress in reducing vitamin-A deficiency among pre-school children over the past 15 years. However, the consumption of vitamin A-rich foods is still low, suggesting that the underlying causes of vitamin A deficiency require further attention.

1.1.8.2 Dietary pattern
The typical rural diet in Bangladesh is, reportedly, not well balanced. Cereals, largely rice, are the main food in Bangladesh. Nearly two-thirds of the daily diet consists of rice, some vegetables, a little amount of pulses and small quantities of fish if and when available. Milk, milk products and meat are consumed only occasionally and in very small amounts. Fruit consumption is seasonal and dietary intake of cooking oil and fat is meager (12). In general, food habits vary at regional and even individual household levels.

1.1.9 Trend of urbanization in Bangladesh and Chronic Diseases
Bangladesh is characterized by low level of urbanization but at the same time it has experienced one of the most rapid urban growths in recent times. The total population of Dhaka, the capital city of Bangladesh, increased from 1.98 million to 9.91 million between 1974 and 2001. It is estimated that by the year 2015 the population of Dhaka will almost double to around 21 million people (13). The increase trend of the urbanization is likely to be fuelled by the movement of poor rural people to towns and cities where they often find shelter in appalling conditions. Chronic diseases are leading causes of morbidity and mortality worldwide (14-16). Mortality from chronic diseases is also increasing in Asia. Chronic diseases account for 70% of all deaths all over the world and Bangladesh as well (17, 18). As the epidemiological transition takes hold, Bangladesh will face greater burden of chronic diseases, such as diabetes, hypertension, cancer and various kinds of degenerative diseases associated with old age.
1.2 Epidemiological Situation of Diabetes Mellitus

1.2.1 Diabetes in Global Overview

According to the official World Diabetes Day (WDD) website, ‘Diabetes is a chronic, potentially debilitating and often fatal disease’. It is now an emerging epidemic worldwide, and it is estimated that globally there are now 246 million people with diabetes, and that this number will rise to 300 million by 2025 (19). The number of people with Diabetes Mellitus (DM) is increasing due to population growth, aging and increasing prevalence of obesity and physical inactivity. Globally, it is ranked as the fourth leading cause of death, in terms of disease (20). It has a high prevalence in both developed and developing countries (21). The World Health Organization (WHO) Report on diabetes prevalence alarmed that diabetes has posed a serious threat to developing countries with respect to their existing health care services (22). Formerly described as a ‘disease of affluence’, it has now become evident that, owing to demographic changes, cultural transition and population ageing, diabetes is now also a ‘developing countries problem’ (23). Important differences are observed in age structure of diabetic population between developed and developing countries. Whereas in the developed world, the majority of diabetics are aged 65 years and above, it was 45-64 years in the developing world (24). The management of diabetes mellitus and the management and prevention of the complications are important challenges of the present time. There are ample evidences from applied clinical research that morbidity and mortality risks associated with diabetes are preventable. Recent epidemiological studies have shown an increased prevalence of diabetes in India (12.1%), Pakistan (11.1%), and China (6.1%) (25-27). Estimated number of diabetics for the South-East Asia Region is 38, 488, 6509. Bangladesh is a developing country that has been facing a high prevalence of diabetes mellitus (DM) and the prevalence of DM is in urban 8.1% and 2.3% in rural areas (28).

1.2.2 Diabetes mellitus in Bangladesh

Magnitude of diabetes mellitus in Bangladesh is increasing. It remains unknown due to lack of countrywide survey. An increasing trend of diabetes registration in all the referral centers in Bangladesh has been noticed in recent years. In Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM),
Dhaka, a total of about 20603 new cases of diabetes are diagnosed every year (29). From Diabetes registry in BIRDEM, it was found that the number of registered diabetic patients in the year 1956 was 39, which has been increased to 15,296 in 1998. At present about 5.6 million are the registered diabetic patients, on average 60% are male and 62% from urban, 32% from rural and 6% from semi-urban area (30).

1.3 Trend of type 2 diabetes in Bangladesh
Socioeconomic and demographic scenario and epidemic transition of Bangladesh shows that diabetes mellitus are increasing in a rapid rate. Health scenario and epidemic transaction: in these days the communicable diseases are declining because of improvement in health service delivery. And due to life style modification, rapid urbanization, less exercise diabetes mellitus are increasing as well. Diabetes mellitus particularly type 2 diabetes is now recognized as a major health problem in Bangladesh. About 90% - 95% of all diabetes patients of Bangladesh belong to Type 2 diabetes (31). Sayeed et al in 1995 conducted a study in rural Bangladesh and found the prevalence of type 2 diabetes was 2.1% (male 3.1% and female 1.3%). Age adjusted (34-64 years of age) prevalence was 2.23% (32). A recent rural study by Sayeed et al in 2003 showed the prevalence of type 2 diabetes was 4.3% and IFG was 12.4% (33). An urban study conducted by Rahim M.A et al in 2000, the prevalence of diabetes was 8.1% (34). Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. It is considered as a compound of complex metabolic syndrome. It can lead to both micro and macro-vascular complications of diabetes mellitus.

1.4 Existing diabetes health care services in Bangladesh
The Diabetic Association of Bangladesh (DAB) plays an unique role in diabetes healthcare delivery in Bangladesh and the association executes its program primarily through its central institute called BIRDEM (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders) a multi-sectoral health care delivery centre founded by National Professor Mohammad Ibrahim in Dhaka in 1980. From 1982 BIRDEM was designated as the WHO Collaborating Centre for Research on prevention and control of Diabetes, Endocrine and Metabolic Disorders. It is
now providing diabetic care to almost 3.5 lakh patients from which about 3500 registered patients are taking health services from BIRDEM OPD every day. As diabetes may affect other system of the body, BIRDEM adopted a multidisciplinary approach to its services. Gradually, BIRDEM established specialized disciplines like, Cardiology, Gastroenterology, Surgery, Gynecology and Obstetrics, Nephrology etc. DAB has a large network of 53 affiliated associations and fourteen NHN (National Healthcare Network) satellite clinics and ten out patients clinics, planned another 500 beds teaching and four 50 beds hospitals in northern district under Health Care Development Project (HCDP) in addition to BIRDEM distributed all over the country.

1.5 Diabetes mellitus
The term "diabetes" refers to a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta cells of the pancreas in Type 1 diabetes with complete insulin deficiency, to abnormalities that result in resistance to insulin action as in Type 2 diabetes. The chronic hyperglycaemia associated with diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. In diabetes, the deficient action of insulin on the target tissues causes the dysfunction of carbohydrate, fat, and protein metabolism (35) It is one of the commonest endocrine disorders. This disease is closely linked to diet and nutrition both in respect to its causation and management. This is a hereditary metabolic disorder and a universal health problem (36).

1.5.1 Types of diabetes
There are two main types of diabetes:

Type 1 diabetes
In Type 1 diabetes or insulin-dependent diabetes, the beta cells in the pancreas that make insulin are destroyed. There is an absolute deficiency of insulin, and people with Type 1 diabetes require insulin injections every day to sustain life. This form of diabetes is more common in childhood and young adulthood but can occur at any age. Poorly controlled Type 1 diabetes leads to early onset of complications.
Type 2 diabetes

People with Type 2 diabetes-usually non insulin-dependent diabetes show resistance to the action of insulin but with persistence of the condition there is also a progressive failure of the pancreatic beta cells and relative insulin deficiency. Type 2 diabetes usually occurs in middle aged and elderly people but its incidence is increasing in younger adults. Most people with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. The condition develops insidiously and the early symptoms may not be recognized. This cluster of risk factors predisposes people with Type 2 diabetes to accelerated microvascular and macrovascular disease (37).

There are also other types of diabetes:

Gestational diabetes: Gestational Diabetes mellitus (GDM) develops in pregnant women and increases the risk for mother and child in the perinatal period. There are usually no symptoms. The condition is detected by screening tests and treatment is generally by diet modification. If blood glucose monitoring shows unsatisfactory control of the condition, insulin injections are advised for the duration of the pregnancy. Women who have had GDM are at future risk of developing Type 2 diabetes.

Secondary diabetes: It covers a group of diabetes where the cause of hyperglycemia can be attributed to factors such as inflammation of the pancreas, or by the use of certain medication such as diuretics or steroids, disease or genetic syndrome (37).

1.6 Complication of diabetes mellitus

Many people with diabetes mellitus eventually develop complications, especially if it is not controlled well. Even if the diabetes is controlled well, complications can still occur. The morbidity and mortality in DM are largely related to chronic complications which are divided in two main groups: macrovascular complications and microvascular complications. Glycemic control is the primary mediator of diabetic microvascular complications and also contributes to macrovascular complications. The high disease burden reflects high rates of microvascular and macrovascular complications from diabetes. It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications, and diminished quality of life. Its microvascular complications include
damage to the eyes, kidneys, and nerves, whereas macrovascular complications include atherosclerosis and other cardiovascular conditions (38).

1.6.1 Macro-vascular complication
Adults with diabetes mellitus frequently develop macrovascular complications. Vascular disease is a frequent cause of morbidity and mortality among patients with diabetes. Diabetes mellitus is a disease associated with several macro-vascular complications including coronary artery disease, cerebrovascular disease and peripheral vascular disease etc. Hypertension and dyslipidemia are the two prominent modifiable factors in the development of these forms of complication in a diabetic person. Heart disease (heart attacks 3-5 times more likely), peripheral vascular disease (amputation 50 times more likely), and stroke (twice as likely) are the major causes of death in patients over the age of 50 than non-diabetics due to increased macro-vascular abnormalities (39).

1.6.2 Micro-vascular complication
The microvascular complications of diabetes encompass long term complications of diabetes affecting small blood vessels (40). It may be present at detection of diabetes. Sometimes, routine/annual health check-up identifies subjects who were not known to be a diabetic. People with diabetes have an increased risk of developing microvascular complications, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy, which, if undetected or left untreated, can have a devastating impact on quality of life and place a significant burden on health care costs. In addition, diabetic microvascular complications can reduce life expectancy. The strongest risk factors are glycaemic control and diabetes duration; however, other modifiable risk factors such as hypertension, hyperlipidaemia and smoking, and unmodifiable risk factors including age at onset of diabetes and genetic factors may all play a part (41).

1.7 Diabetic Retinopathy
Diabetic eye complications and, in particular, diabetic retinopathy (DR) is one of the major microvascular complications of diabetes. It is a vascular disorder affecting the microvasculature of the retina (42). Diabetes can affect sight by causing cataracts, glaucoma, and most importantly, damage to blood vessels inside the eye, a condition
known as "diabetic retinopathy". It is a common complication of diabetes that is caused by changes in the blood vessels of the retina. When blood vessels in the retina are damaged, they may leak blood and grow fragile, brush-like branches and scar tissue. This can blur or distort the vision images that the retina sends to the brain (43). If untreated, it may lead to blindness. If diagnosed and treated promptly, blindness is usually preventable.

1.7.1 The Epidemiology of Diabetic Retinopathy
Diabetic retinopathy (DR) is the most significant cause of visual impairment and blindness, thereby reducing the quality of life and serious economic and social consequences. It is estimated that diabetes mellitus affects 4 per cent of the world’s population, almost half of whom have some degree of DR at any given time (42). DR occurs both in type 1 and type 2 diabetes mellitus and has been shown that nearly all type 1 and 75 per cent of type 2 diabetes will develop DR after 15 yr duration of diabetes as shown in earlier epidemiological studies (44, 45). DR is among the leading causes of blindness in people of working age, affecting both the genders equally (46, 42). A diabetic is 25 times more likely to go blind than a person in the general population. DR is responsible for 4.8% of the 37 million cases of blindness due to eye diseases. The proportion of blindness due to diabetic retinopathy ranges from close to 0% in most of Africa, to 3–7% in much of South-East Asia and the Western Pacific, to 15–17% in the wealthier regions of the Americas, Europe and the Western Pacific (47).

1.7.2 Pathogenesis of diabetic retinopathy
The pathogenesis of DR is multi-factorial, but is primarily caused by the metabolic effects of chronic hyperglycemia. Chronic hyperglycemia is thought to be the primary cause of diabetic retinopathy (48). Many studies have demonstrated that duration of diabetes, chronic hyperglycemia, as well as hyperlipidemia and hypertension, contribute to the pathogenesis of DR. The exact mechanisms by which elevated glucose initiates the vascular disruption in retinopathy remain poorly defined, and, not surprisingly, several pathways have been implicated (49). Nonproliferative retinopathy develops first. Proliferative retinopathy is more severe and may lead to vitreous hemorrhage and retinal detachment.
1.7.3 Causes of Diabetic Retinopathy

Diabetic retinopathy is the result of damage caused by diabetes to the small blood vessels located in the retina. Blood vessels damaged from diabetic retinopathy can cause vision loss:

- Fluid can leak into the macula, the area of the retina which is responsible for clear central vision. Although small, the macula is the part of the retina that allows us to see colors and fine detail. The fluid causes the macula to swell, resulting in blurred vision.
- In an attempt to improve blood circulation in the retina, new blood vessels may form on its surface. These fragile, abnormal blood vessels can leak blood into the back of the eye and block vision. (50)

1.7.4 Classification of Diabetic Retinopathy

The Airlie House classification (51), proposed in the late 1960’s and still used by clinicians world-wide, distinguishes two patterns of retinopathy, NPDR (or background retinopathy) and PDR.

- **Nonproliferative retinopathy** is the earlier stage. In this stage there may be hemorrhages (bleeding) in the retina with leakage of blood causing a "wet retina" or protein deposits (exudates) in the retina. As a consequence, the retina does not receive enough oxygen. This early stage of diabetic retinopathy usually produces no visual symptoms but, if there is fluid in the central portion of the eye (macular edema), vision is diminished.

- **Proliferative retinopathy** is the second stage. New abnormal vessels develop in the retina and grow towards the center of the eye. These vessels frequently bleed into the vitreous (the clear jelly in the center of the eye). Such bleeding episodes cause severe visual problems. Small bleeds may clear up on their own but larger bleeds need surgery. The abnormal vessels may also produce large scars in the retina that may cause the underlying retina to detach (retinal detachment).
1.7.5 Screening for diabetic retinopathy

Diabetic retinopathy is a leading cause of adult blindness, and screening can reduce the incidence. Screening just increases the chances that a condition will be avoided, found early, or are able to be cured. It is widely recommended that all persons with diabetes mellitus should be regularly screened for diabetic retinopathy (52). Two recent developments have increased the potential for primary care physicians to screen for diabetic retinopathy with greater accuracy and efficiency. First, a simple prediction rule has been developed that accurately predicts vision-threatening diabetic retinopathy by viewing lesions in a limited number of retinal fields. Second, a new-generation ophthalmoscope has been developed that allows viewing of these retinal fields without dilation (53). Screening programmes detect some conditions, reduce the chance of developing or dying from some conditions, and can improve the quality of life.

1.7.6 Eye care services in Bangladesh

BIRDEM is a multidisciplinary centre primarily designed to treat the diabetic patients. Presently it has emerged as one of the biggest centre for medical and research facilities in Bangladesh. The department of Ophthalmology is the most developed and sophisticated centre in this country. Here, fluorescein angiography, laser treatment, vitreoiretinal surgery, glaucoma and cataract surgery with intraocular lens implantation are routinely done on diabetic and non-diabetic patients. The department of Ophthalmology has a long experience with diabetic retinopathy and its management in Bangladesh. In Bangladesh laser treatment for diabetic retinopathy was first started at BIRDEM in 1980. Since then this department has successfully treated more than 20,000 eyes with diabetic retinopathy. Being a developing country this department has developed their own protocol for the management of these patients.
Chapter 2
Justification of the study, Research Questions and Objectives
2. Justification of the study, Research questions and Objectives

2.1 Justification of the study
Many cross sectional studies have been done on the prevalence as well as the associated risk factors for developing DR. Due to inadequacy of prospective studies performed in this field the casual roles of risk factors have been difficult to be ascertained. In Bangladesh hospital based data on the prevalence of and factors associated with DR are still lacking. Large scale prospective studies in specific racial and environmental perspectives may give valuable information on the role of various risk factors of DR in that particular population. In the above context, this research work is attempting an epidemiological study to make a baseline survey focused on DR. In addition, accurate identification of risk factors responsible for diabetic retinopathy is essential if effective preventative measures are to be developed.

2.2 Research Questions
- What is the incidence rate of DR 15 years after diagnosis among Bangladeshi type 2 diabetic patients?
- What are the risk factors for developing DR among Bangladeshi type 2 diabetic patients?
- What is the relationship of socio-demographic, anthropometric, clinical, nutritional, biochemical parameters with DR and NDR among Bangladeshi type 2 diabetic patients?

2.3 Objectives of the study subjects

2.3.1 General objective
To estimate the incidence of and factors associated with diabetic retinopathy among type 2 diabetics.
2.3.2 Specific objectives

- To investigate the 5 year, 10 year and 15 year incidence rate of diabetic retinopathy in Bangladeshi type 2 diabetic patients (Paper I).

- To identify the risk factors for developing DR and to examine the relative association between socio-demographic, anthropometric, clinical, nutritional and biochemical parameters and DR among Bangladeshi type 2 diabetic patients (Paper II).
Chapter 3
Materials and Methods
3. Materials and Methods

3.1 Study population

The study population was Bangladeshi men and women aged thirty years and above with type 2 DM patients, newly registered at BIRDEM in 1993 included in this study.

3.2 Study design

Historical cohort study was designed to collect data which was fully quantitative and retrospective in nature. To collect necessary information the population material was drawn from patient registry book in 1993 and followed since 1993 to 2008. The study design is outlined in Figure 1.

![Flow Chart of Patient recruitment and follow-up](image_url)

Figure 1: Flow Chart of Patient recruitment and follow-up.
3.3 Study setting
The study was conducted in the BIRDEM, the central institute of the Diabetic Association of Bangladesh, has a registered base of about 3,70,000 diabetic patients (> 95% type 2 DM) and its OPD is visited by about 3000 patients every day (with around 80 new patients registered daily). BIRDEM is the tertiary level hospital and has specialized care system for diabetes, quite a significant number of patients with diabetes come to BIREDEM hospital from all over the country including Dhaka city.

3.4 Selection Criteria of Tertiary Hospital (BIRDEM)
Criteria for selection of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) for study: it has been recognized nationally and internationally as a centre of excellence for medical services and research. From 1982 BIRDEM was designated as the WHO Collaborating Center for research on prevention and control on Diabetes, Endocrine and Metabolic Disorders. It is in the capital city Dhaka where the population density is highest and where previous studies relating to diabetes had been carried out and where the prevalence of diabetes was expected to be highest. Finally data of diabetic patients are properly recorded and preserved in this hospital.

3.5 Inclusion criteria
All registered diabetic patients both male and female aged more than 30 years were selected for this study.

3.6 Exclusion criteria
Type 1 Diabetic, Gestational Diabetic cases and dropped out cases those who failed to follow up at least 15 years were excluded from this study.

3.7 Sample size and sampling Technique
The size of the sample of the population in a study is one of the main concerns in determining whether an observed association between exposure and outcome is due to chance alone. In order to determine required sample size for this study, the Student’s formula was used.
\[ n = \frac{z^2 pq}{d^2} \]
Where, \( z = 1.96 \), \( p = \) prevalence of diabetic retinopathy from a previous study on hospital based population in Nepal (54); 44.7% i.e. \( p = 0.447 \), \( q = (1 - p) \) i.e. \( 0.553 \) and \( d = \) allowable error of known prevalence i.e. \( 0.07 \) (0.447). Ideally, it should be \( 0.05 \) (0.447); but, to be on safe estimation with minimum sample size we allowed only 7% error of prevalence.
Thus, \[ n = \frac{(1.96)^2 (0.447) (0.553)}{[(0.07) (0.447)]^2} \]
Or, \[ 0.9492/ 0.000979 = 970. \]
The study subjects were randomly selected.

3.8 Data Collection Procedures
Data were collected from the hospital registry, patient’s diabetic guide book and also through a self reported information questionnaire, clinical examinations and anthropometric measurements.

3.8.1 Hospital Registry
Hospital registry is originally the place where the patient information is collected (in registers). The register includes almost all people who have been diagnosed with diabetes. All patient records in BIRDEM are preserved and unauthorized accesses to these records are prohibited. A registry is usually organized so the data was collected from this registry and analyzed.

3.8.2 Diabetic guide book
Socio demographic, anthropometric, medical history, clinical and laboratory findings and treatment on diabetes are recorded systematically in this book developed by Diabetic Association of Bangladesh (Annex-2). A detailed history of disease onset & the illness were taken from this patient’s diabetic guide book.
3.8.3 Questionnaire

A structured questionnaire (Annex-1) was developed and translated into Bengali language (local language) and revised after pre-testing. The questionnaire contains four part; 1. socio-economic and general information, 2) anthropometrical measurements and history of DR 3) investigation report of biochemical and clinical measurements, 4) history of dietary intake and physical exercise were taken from the subjects.

3.8.4 Anthropometric measurements

Anthropometric measurements such as weight, height, waste and hip circumferences were taken from the patients. These measurements was done using standardized methods (Aspray et al 2000, WHO 2003). Body weight in light clothes was measured to the nearest 0.1 kg using a Sohenle mechanical weighing scale (Soehnle-Waagen GmbH & Co. KG, Wilhelm-Soehnle-Strabe 2, D-71540 Murrhardt/Germany) and the height to the nearest 0.5 cm using a portable, locally manufactured, stadiometer, with subjects, standing upright on a flat surface without shoes, the back of the heels and the occiput on the stadiometer. Waist circumference, were taken midway between the lowest rib and the iliac crest and hip circumference at the level of the greater trochanters was measured to the nearest mm using a flexible tape. Body Mass Index (BMI), calculated as the ratio of weight in kilograms over height in meters squared, \[\frac{\text{weight (kg)}}{\text{height (m)}}\]. The definitions of overweight and obesity was based on BMI \(\geq 25 \text{ kg/m}^2\) and \(\geq 30 \text{ kg/m}^2\) respectively (55).

3.8.5 Measurement of blood pressure

Three readings of blood pressure, at 10 minutes interval were taken from each participant. Measurements was taken on participant on a sitting position after 5 minutes rest, by trained and certified health workers following AHA procedures, using electronic AND 0 78 Model UA-767 fully automatic, clinically validated digital BP monitor (A & D Company Limited Tokyo, Japan), with a suitable sized cuff (Small 9x18 cm, medium 12x23 cm and large 15x33 cm) at the forearm. Hypertension was deemed to be present when the systolic pressure was greater than 140 mmHg or when the diastolic pressure was greater than 90 mmHg (37).
3.8.6 Recording of dietary intake and energy expenditure

Using 24 hr-recall method for the dietary history of the subjects were collected. In the 24 hr-recall method the subjects are asked by the health worker to recall the subject’s exact food intake during the previous twenty-four-hour period. Food list album (Annex-3) and the food stuff (plate, glass, spoon) were also used for this dietary history. Energy expenditure of the subjects was also recorded in this study. It was calculated by factorial method (WHO/FAO/UNU 1985).

3.8.7 Biochemical measurements

A fasting serum sample was drawn from all individuals for the levels of the biochemical parameters using the following methods.

Plasma glucose was estimated by Glucose-Oxidase method by an Auto analyzer (Auto lab, Analyzer Medical System, Rome, Italy) using reagents of Randox Laboratories, UK. Percentage of HbA\textsubscript{1c} in whole blood was estimated by the VARIANT Hemoglobin A\textsubscript{1c} Program using a modified HPLC method. Fasting plasma glucose $\geq 7$ mmol/L, 2-hr post glucose load $\geq 11.1$ mmol/L (37) and Hemoglobin A\textsubscript{1c} $>7\%$ (56) were considered as a type 2 diabetic patient in this study. Plasma triglyceride (TG) was measured by enzymatic colorimetric method in the Automatic Analyzer, Hitachi 704, Hitachi Ltd., Tokyo, Japan using reagents of Randox Laboratories Ltd., UK. Plasma total cholesterol (TC) was measured by enzymatic endpoint method in the Automatic Analyzer, Hitachi 704, Hitachi Ltd., Tokyo, Japan using reagents of Randox Laboratories Ltd., UK. Plasma high density lipoprotein (HDL) was measured by enzymatic colorimetric method in the Automatic Analyzer, Hitachi 704, Hitachi Ltd., Tokyo, Japan using reagents of Randox Laboratories Ltd., UK. LDL-cholesterol in plasma was calculated by using the formula:

\[ \text{LDL cholesterol} = \text{TC} - (\text{TG}/5 + \text{HDL cholesterol}) \]

Lipid abnormalities were deemed to be present when the TC was $>200$ mg/dl, TG was $>150$ mg/dl, LDL was $>100$ mg/dl, HDL was $<40$ mg/dl for men and $<50$ mg/dl for women. Estimation of serum creatinine was done by alkaline-picrate methods using reagents of Randox Laboratories, UK. The presence of nephropathy was considered when the serum creatinine level was $>1.5$ mg/dl (56).
3. 9 Eye Examination Methods

Visual acuity (VA) of each eye was tested separately by using Snellen distance vision chart at 6 meters (57). Slit lamp examination was performed to document any abnormality in the anterior segment. Intraocular pressure was measured using a Schiotz tonometer before dilating the pupils. The retina specialist or senior ophthalmologist reconfirmed all the clinical findings. Fundus photography (58) was also taken to confirm the diagnosis as required. After complete eye examination, the necessary treatment was provided.

3.10 Training of health personnel and piloting of tools

Three days training (both theoretical and practical) was provided to the health workers by the principle investigator for the use of research tools and procedures. The training focused on the demonstration of the questionnaire, collection of information from the hospital records, measurement of anthropometric and history of dietary intake, approach of communication and ethical issues. A small pilot study was conducted on 10 subjects. All the operational data collection tools were piloted in the study site, and amended accordingly. The intention was to identify the possible problems to collect data necessary for the study.

3.11 Diagnosis criteria used for diabetes mellitus in Bangladesh

In BIRDEM, diagnosis is based on documentation of glucose intolerance in the patients according to the WHO recommended criteria. The values of diagnostic criteria are described in the following table (1).
Table 1: Values for diagnosis of diabetes mellitus and other categories of hyperglycemia. Glucose concentration mmol/l (mg/dl)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Whole Blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Venous</td>
<td>Capilary</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>≥6.1 (≥110)</td>
<td>≥6.1 (≥110)</td>
</tr>
<tr>
<td>2-h post glucose load or both</td>
<td>≥10.0 (≥180)</td>
<td>≥11.1 (≥180)</td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance (IGT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (if measured)</td>
<td>&lt;6.1 (&lt;110)</td>
<td>&lt;6.1 (&lt;110)</td>
</tr>
<tr>
<td>2-hr post glucose load</td>
<td>≥6.7 (≥120)</td>
<td>≥7.8 (≥140) and &lt;11.1 (&lt;200)</td>
</tr>
<tr>
<td>and &lt;10.0 (180)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impaired Fasting Glycemia (IFG)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>≥5.6 (≥100) and &lt;6.1 (&lt;110)</td>
<td>≥5.6 (≥100) and &lt;6.1 (&lt;110)</td>
</tr>
<tr>
<td>2-hr post glucose load (if measured)</td>
<td>&lt;6.7 (&lt;120)</td>
<td>&lt;7.8 (&lt;140)</td>
</tr>
</tbody>
</table>

*Source: WHO, Department of Noncommunicable disease surveillance, 1999 (37).*
3.12 Diagnosis of Diabetic Retinopathy in Bangladesh

Diabetic retinopathy was diagnosed through a comprehensive eye examination - testing, with special emphasis on evaluation of the retina and macula, included: (57, 58)

- Patient history with their presence of diabetes and other general health condition was taken to determine vision difficulties.
- Visual acuity was measured to determine the extent of affected central vision.
- Refraction was done to determine any kind of changes in prescription for an eyeglass.
- Evaluation of the ocular structures, including the evaluation of the retina through a dilated pupil was performed.
- Pressure within the eye was measured.

Supplemental testing was also done, including:

- Retinal photography or tomography to document current status of the retina.
- Fluorescein angiography to evaluate abnormal blood vessel growth.

3.13 Screening for diabetic retinopathy in Bangladesh

Diabetic retinopathy is the only blinding ocular disease where severe visual loss can be avoided by retinal photocoagulation provided the screening protocol, photocoagulation indications and treatment patterns are properly followed. Any patient attending BIRDEM out patient department (OPD) directly or referred by the doctors from different diabetic hospitals or other hospitals undergo medical evaluation in details. If diabetic is detected, they are referred to the department of ophthalmology. In eye out patient department a medical officer evaluates the patient first as the following protocol.
3.13.1 Protocol for screening of diabetic eye complications

- Identification and collection of clinical data.
- Onset of visual symptoms.
- History of glaucoma.
- Measurement of best corrected visual acuity.
- Pupil dilation.
- Lens examination by slit lamp.
- Fundus examination in detail.
- Fluorescein angiography and colour fundus photography done when indicated.

If any retinopathy is detected the patient is referred to the consultant clinic. Here the patient is further evaluated and is managed as the management schedule.
3.14 Conceptual Framework

Independent Variables

**Demographic and Socio-economic Factors**
Age, Sex, Area, Occupation, Education, Income

**Anthropometrical and Nutritional Factors**
BMI, Dietary Intake

**Clinical and Biochemical factors**
Blood Pressure, FBG, 2-hr ABF, Hemoglobin A1c, Lipid Profile, Creatinine, SGPT

Dependent Variables

Diabetic Retinopathy
3.15 Data management and analysis

Data were first compiled through a custom made software developed by the Information Management Unit of the Hospital. Those were edited, classified and coded on same day for completeness and accuracy of the data. Data were then imported into SPSS version 12.0 (Statistical Package for Social Science), by IT department in Bangladesh. Descriptive statistics were presented using frequency table and cross tabulations. The formula (59) was used to estimate stratified incidence rate per 1000 person-years and 95% confidence intervals. For time consuming the formula was put into SPSS 16.0 using syntax to perform the calculation. Means and standard deviations were presented for continuous variables. Student’s t test was used to assess the differences between Diabetic Retinopathy (DR) and No Diabetic Retinopathy (NDR). Univariate and multivariate generalized linear models were used to assess associations of clinical, biochemical and anthropometric variables with retinopathy. The associations were presented in form of relative risks (RRs) and 95% Confidence Intervals (CIs). When the univariate analyses showed significant relationships (p < 0.25) between exposure variables and retinopathy, these exposure variables (risk factors) further were included into the multivariate analysis (final model). The p-values less than 0.05 were considered statistically significant. All p-values presented are two tailed. The data were analyzed using a computer program Statistical Package for Social Science (SPSS) (Windows version 16.0).

3.16 Ethical issues

Ethical clearance was obtained from the Ethical Review Committee (ERC) in Norway and from the Diabetic Association of Bangladesh (DAB) before commencement of the study. Ethical guidelines of Declaration of Helsinki IV (2001) were followed throughout the study. All patient records in BIRDEM are preserved and unauthorized accesses to these records are prohibited. Since the patient data was used in this study, the subjects’ personal information was kept confidential. The confidentiality of using her/his records was emphasized and the rationale for the present clinical examinations and investigations was explained. There was no possibility of harming the patients or the institute by the analysis of these recorded data. Informed written consent (Annex-4) was taken at the time.
of enrolling the patients. The rationale and objective of the project was written in plain and simple Bengali language and each patient was briefed about the benefits and risks of the project. All patients were informed that they were free to leave or to refuse to take part in the research at any time. Each patient was given a separate identify number. No undue incentive was given to the patient.
Chapter 4

Summary of Results
4. Summary of Results

4.1 PAPER I

Incidence of Diabetic Retinopathy amongst type 2 diabetic patients in Bangladesh -a hospital based study

The paper attempts to estimate the 5 year, 10 year and 15 years of incidence rate of diabetic retinopathy in Bangladeshi type 2 diabetic patients. This study was conducted among newly diagnosed type 2 diabetic patients who had visited the Out Patient Department of BIRDEM Hospital (the tertiary hospital of the Diabetic Association of Bangladesh) Dhaka, Bangladesh. In this historical cohort study a group of 977 Bangladeshi type 2 diabetic subjects, aged 30 years and above, who were first diagnosed, free of any ocular complain and regularly followed in the Outpatient Department of BIRDEM during 1993 to 2008, were randomly recruited.

WHO criteria was used for diagnosis and defining the diabetes state in this study population. The incidence rates of DR were calculated by the formula (59) and then put into the syntax to perform the calculation. It was expressed as per 1000 person-years with 95% confidence intervals (CIs). Diabetic Retinopathy was graded using the Early Treatment Diabetic Retinopathy Study. After obtaining informed consent from each patient, all patients were examined by an ophthalmologist and were reconfirmed by a senior ophthalmologist. Detailed demographic, socio-economic information, history of disease onset & the illness were taken from the patient’s diabetic guide book and medical records.

In 1993, 12,232 diabetic subjects were registered in this hospital; by random allocation 1303 patients were recruited. Among them 1198 were type 2 and 105 were type 1 diabetic patient. Out of 1198 subjects, 977 were participated in this study and 221 were lost to follow-up. Of the 977 newly diagnosed type 2 diabetic subjects, 468 were male and 509 were female (mean ±SD, age 56 ±8 years).
According to the age distribution of the study subjects the age groups were <45 (115/12%), 45-60 (617/63%) and >60 (245/25%) years respectively. Most of the study subjects (784/80%) came from urban area; from rural was 14% and semi-urban 6%.

Among the subjects Muslim was 93%, Hindu 7% and 38% were employed in service whereas unemployed 62%. The study subjects are divided into three groups according to their education and income level. Among them Illiterate 6%, Under Graduate 63% and above Graduate 31%; and the income level were poor 24%, medium 52% and high 24% respectively.

At 15 years of follow-up, 11.8% DR was found in first 5 years and it was nearly double (17.5% to 32.2%) in ten years to fifteen years. Among the patients, non proliferative DR (NPDR) was found in 115 patients (11.8%) at 5 years. But at 10 years it was found that 136 (13.9%) had mild, 14 (1.4%) had moderate and 1 (0.1%) had severe NPDR; whereas at 15 years 111 (11.4%) had mild, 77 (7.9%) had moderate, 33 (3.4%) had severe, 5 (0.5%) had very severe NPDR and 3 (0.3%) had early PDR.

The study revealed that the incidence rates of DR and (95% CI) were 23.54 (19.61-28.26), 17.52 (14.93-20.55) and 21.47 (18.86-24.44) per 1000 person-years at 5, 10 and 15 years respectively. The incidence of DR was higher at first 5 years than 10 years but the trend was also increased at 15 years near to 5 years.

In 5 years incidence showed clear trend by age, being 1.74 (95% CI, 0.24-12.35) at <45 years; 18.48 (14.25-23.95) at 40 to 60 years; 46.53 (35.89-60.32) at >60 years of age. The females had higher incidence of DR in all age categories compared to males (2.56; 95% CI, 0.36-18.20 vs 0; 21.64; 15.68-29.86 vs 14.44; 9.38-22.55; and 49.44; 32.55-75.08 vs 44.87; 32.22-62.50). Similar trend was noted in the 10 year that incidence of DR increased with increasing age, being 12.28 (7.27-20.74), 16.79 (13.71-20.55) and 22.87 (16.96-30.84) for the respective age groups. This was also more prominent in female subjects in all age groups compared to males (14.29 vs 8.11; 16.72 vs 16.86; 29.85 vs 19.01 in all age group respectively). And finally in 15 years incidence of DR increased by age, being 18.00 (12.34-26.25) at <45 years; 22.17 (18.94-25.96) at 45-60 years and
21.61 (16.24-28.76) in the oldest age group. Female had considerably higher incidence compared to male at <45 years of age (19.19; 12.24-30.09 vs 15.69; 7.84-31.37).

4.2 PAPER II

Risk factors for Diabetic Retinopathy among Bangladeshi diabetics

The objective of the study was to identify the risk factors for developing diabetic retinopathy (DR) and to examine the relative association between socio-demographic, anthropometric, clinical, nutritional, biochemical parameters and DR among Bangladeshi type 2 diabetic patients.

A total 1198 patient with newly diagnosed type 2 diabetics were randomly recruited during 1993 to 2008. Among them, 101 had died, 87 could not be located, 37 were refused and 977 were studied in this follow-up who was free of DR in both eyes at baseline (1993).

In this hospital-based historical cohort study, we measured fasting blood glucose, 2-hr ABF, HbA1C levels, lipid profile (TC, TG, LDL-C and HDL-C), blood pressure, anthropometrical indicators (ht, wt, waist and hip circumference), dietary intake and physical activity level. WHO criteria was used for diagnosis and defining the diabetes state in this study population. Diabetic Retinopathy (DR) was diagnosed by retinal color photography and classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS). All patients were examined by an ophthalmologist and were reconfirmed by a senior ophthalmologist. Detailed demographic, socio-economic information, history of disease onset & the illness were collected from the patient’s diabetic guide book and medical records. Informed consent was taken at the time of enrolling the patients.

Student’s t test was performed to compare with Diabetic Retinopathy (DR) and No Diabetic Retinopathy (NDR). Univariate and multivariate generalized linear models were used to assess associations of clinical, biochemical and anthropometric variables with retinopathy. The relative risk (RRs) as well as the 95% CIs was also calculated. When the univariate analyses showed significant relationships (p < 0.25) between exposure variables and retinopathy, these exposure variables (risk factors) further were included into the multivariate analysis (final model). The p-values less than 0.05 were considered
statistically significant. All p-values presented are two tailed. The data were analyzed using a computer program Statistical Package for Social Science (SPSS) (Windows version 16.0).

UNIVARIATE ASSOCIATION OF RETINOPATHY WITH CLINICAL, BIOCHEMICAL, NUTRITIONAL VARIABLES

Among patients with complete follow-up data, high levels of mean fasting blood glucose (11.0±3.7 vs 8.6±2.9, 10.5±2.7 vs 8.5±2.5 and 10.91±3.1 vs 7.4±1.8 mmol/L, respectively; P<0.05), 2-hr ABF (16.06±4.8 vs 13.2±4.2, 15.4±3.8 vs 12.9±3.8 and 16.5±4.1 vs 11.7±2.7 mmol/L, respectively; P<0.05) and HbA1c ((9.6±2.6 vs 7.7±2.3, 9.9±2.1 vs 8.0±2.3 and 10.38±2.1 vs 7.27±1.5%, respectively; P<0.05) was found to be significantly higher in DR compared to NDR subjects at the level of 5, 10 and 15 years.

It was found that serum cholesterol in 10, 15 years (210.0±42.9 vs 198.7±43.0, 216.4±45.1 vs 204±40.5 mg/dl, respectively; P<0.05); serum triglycerides in 5 (199.4±88.5 vs 170.7±71.9 mg/dl, P<0.05), 15 years (200.0±86.4 vs 180.1±70.5 mg/dl, P<0.05) and LDL-cholesterol concentrations (137.8±43.4 vs 130±38.5 mg/dl, P<0.05) in 15 years were significantly higher in subjects with DR compared to NDR, while HDL-cholesterol concentrations were similar in the two groups in three different time periods.

We have observed that systolic (130±12.3 vs 126±11, 129±11.7 vs 125±10.8 and 132±11.2 vs 123±9.1 mmHg, respectively; P<0.05) and diastolic blood pressure (84±8.31 vs 80±7.5, 83±7.0 vs 81±7.6 and 85±6.0 vs 79±5.6 mmHg, respectively; P<0.05) was significantly higher in DR groups than NDR in 15 year follow-ups.

Serum creatinine was also found to be significantly higher DR compared to NDR subjects at the level of 5, 10 and 15 years (1.15±0.35 vs 1.07±0.3, 1.36±0.44 vs 1.14±0.37 and 1.8±0.74 vs 1.11±0.42 mg/dl, respectively; P<0.05).

In our study BMI, PAL and dietary intake (both macro and micro nutrient) did not differ significantly between the groups in 15 year follow-ups. Except the fiber intake was significantly lower (5.97±2.42 vs 6.50±2.52 g/day, P=0.008) in DR compared to NDR groups.
By univariate analysis, it was shown that the risk of DR was increased by 7.2%, 2.5% and 0.3% respectively when age was increased by 1 year in 15 year follow-ups. Age was found to be significant association with DR in first 5 (P<0.00, RR= 1.072 in 95% CI: 1.05-1.09) and 10 years (RR= 1.025 in 95% CI: 1.00-1.04) after diagnosis. Sex, education and the level of income were not associated with DR in different three time periods. The risk of DR was significantly higher in urban population (P<0.00, RR= 1.76 in 95% CI: 1.2-2.4) compared to semi-urban and village in 10 years. On the other hand, a significant protective effect was shown in the employed subjects compared to unemployed subjects at first 5 years (P<0.00, RR= 0.40 in 95% CI: 0.2-0.6 and P<0.05, RR= 0.59 in 95% CI: 0.3-0.9).

The patients having FBG≥7 mmol/L, the risk for DR was almost 4, 3 and 5 times significantly higher than the patient had FBG<7 mmol/L and 2-hr ABF was shown 3.46, 3 and 6 times significantly higher who had≥11.1 mmol/L compared to the normal level in 15 years follow-ups. On the other hand, HbA1C levels ≥7 (%) was also found 3.7, 8.3 and 7.4 times significantly higher for the development of DR during the study periods compared to those had <7 (%).

In univariate model, serum triglycerides level those who had ≥150 mg/dl was significantly higher (P<0.01, RR= 1.56, 1.50 and 1.37 times, respectively) in 5, 10 and 15 years and patient had≥200 mg/dl serum cholesterol was significantly higher (P<0.05, RR= 1.36 in 95% CI: 1.0-1.8) in 10 years compared to the normal level, while LDL and HDL-cholesterol were not statistically significant for the development of DR in 15 year follow-ups. But the high levels of LDL and low level of HDL were found to be higher risk to develop DR in 15 years follow-up. Patients having the serum creatinine level ≥1.5 mg/dl it was found to be 3.15 (P<0.00, CI: 2.3-4.1 and CI: 2.0-3.5) times higher in 10 years and 4.64 times higher (p<0.00, CI: 3.7-5.6 and CI: 3.8-5.7) in 15 years compared to the normal levels.
Systolic hypertension was found to be significantly associated with DR in different three time periods (RR= 2.19, 1.81 and 2.59 respectively) and diastolic hypertension showed 3.43 and 2.03 (P<0.00, CI: 2.2-5.2 and 1.4-2.7) times higher risk for the development of DR in first 5 and 15 years follow-up.

**MULTIVARIATE ASSOCIATIONS OF RETINOPATHY WITH CLINICAL, BIOCHEMICAL AND ANTROPOMETRIC VARIABLES**

Multivariate analysis showed that age was found to be significant association with DR in first 5 years (P<0.00, RR= 1.06 in 95% CI: 1.04-1.08) and female had slightly higher risk to develop DR compared to males.

Among the semi-urban subjects the risk of DR was observed to be higher during the study periods and it was significantly higher (P<0.05, RR= 1.83 in 95% CI: 1.0-3.1) at the level of 10 years compared to urban and village. A significant protective effect was also shown (P<0.05, RR= 0.59 in 95% CI: 0.3-0.9) in the employed subjects compared to unemployed subjects at first 5 years.

In multivariate analysis the risk for DR was found to be significantly 3.19 (CI: 1.7-5.8), 2.55 (1.5-4.3) and 2.99 (CI: 1.9-4.7) times higher who had FBG≥7 mmol/L compared to the normal levels during three different time periods. On the other hand, those had the level ≥7 (%) was found 8.34 (3.7-18.6), 3.45 (1.6-7.3) and almost 5 times (CI: 2.8-8.5) significantly higher for the development of DR compared to those had <7 (%) in 5, 10 and 15 years.

We did not observe any significant association with TC and TG for the development of DR, but the risk of DR was notably higher who were not in normal range of TC and TG in this follow-up study.

Patients having the serum creatinine level≥1.5 mg/dl it was found to be 2.66 (P<0.00, CI: 2.0-3.5) times higher in 10 years and 4.67 times higher (p<0.00, CI: 3.8-5.7 adjusted for age) in 15 years compared to the normal levels.
It was observed that hypertension was significant association with DR in first (P<0.05, RR= 1.67 in CI: 1.0-2.6) and 15 (P<0.00, RR= 2.63 in 2.1-3.2, adjusted for age) years after diagnosis.

In univariate and multivariate analysis, we did not find any association with BMI for the occurrence of DR but protective effect was shown with BMI <18.5 compared to those with BMI 18.5-24.99 (normal) in 15 year follow-ups. However the risk of DR was notably higher for obese individuals but significant association was not noted because of fewer subjects belonging in this group.
Chapter 5
General Discussion
5. General Discussion
5.1 Methodological Consideration

5.1.1 Study Design
A hospital based historical cohort study was chosen in order to investigate the risk factors that may be associated with the occurrence and increment of DR among type 2 diabetic patients in Bangladesh. The measure of disease in cohort studies is the incidence rate, which is the proportion of subjects who develop the disease under study within a specified time period (60). On the other hand, cohort studies are stronger in establishing causal relationships because the confounding variables are to a large extent eliminated. A population based study would have been more appropriate to establish epidemiological causation of risk factors and the incidence of DR. But such type of study is very time and resource intensive. The hospital based study is the most convenient way to select a group of diabetic patients and data from this historical cohort study may also help to develop hypothesis regarding the involvement of different risk factors of DR in this population.

5.1.2 Selection of hospitals (BIRDEM)
From 1982 Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) was designated as the WHO Collaborating Center for research on the prevention and control of Diabetes, Endocrine and Metabolic Disorders. It is in the capital city Dhaka where the population density is the highest and where previous studies relating to diabetes had been carried out. The prevalence of diabetes was expected to be highest in this location. It is now providing diabetic care to almost 350,000 patients from which about 3000 registered patients are taking health services from BIRDEM OPD every day. This hospital delivers standard diabetes care to all groups of diabetic patients and data of diabetic patients are properly recorded and preserved in this hospital. The department of Ophthalmology of BIRDEM is the most developed and sophisticated centre in this country. Here, fluorescein angiography, laser treatment, vitreoretinal surgery, glaucoma and cataract surgery with intraocular lens implantation are routinely done on diabetic and non-diabetic patients. The department of Ophthalmology has a long experience with diabetic retinopathy and its management in Bangladesh.
5.1.3 Diagnosis criteria used for DM and DR in Bangladesh

In BIRDEM, diagnosis of diabetes is made by the reporting physician according to the World Health Organization (WHO) criteria (37). It is made in each case by a standard oral GTT with 75gm glucose load for type 2 diabetes. DR is diagnosed through a comprehensive eye examination. The ophthalmologic examination includes best corrected visual acuity (57), slit-lamp biomicroscopy, applanation tonometry and also detailed fundus examination (58) by both indirect ophthalmoscopy and contact lens biomicroscopy (with pupils dilated) conducted by retinal specialist. The grading of retinopathy is defined according to the modified Airlie House classification adopted by the Early Treatment Diabetic Retinopathy Study (61). We conducted our study based on these diagnosis criteria.

5.1.4 Sample size and sampling technique

In order to determine the sample size, the Student’s formula was used and we calculated the sample size 960 for this study. Due to patient drop-out we selected about 1200 type 2 diabetic patients by simple random procedures from OPD of BIRDEM based on records during 1993-2008. Among them nine hundred seventy seven patients were studied who was free of any ocular complains in both eyes in this 15 year follow-up. With simple random sampling, every person or each item in a population has an equal chance of inclusion in the sample (62). In this study it was possible to include a good number of sample according to our estimates, thus this sample size enabled us to analyse and interpret the result in most of the circumstances.

5.1.5 Follow-up rate of the participants and data collection

In this study the follow-up rates of the participants was 81% which represents relatively few drop-out during the study period. On the other hand, we depended on the information of medical records or hospital registry which is sometimes insufficient and incomplete. Therefore, we chose to interview the patients and able to recheck those medical records from patients’ diabetic guide book.
5.2 Methodological Discussion
5.2.1 Strength of the study
5.2.1.1 Pretest
A pretest was undertaken in 10 subjects to examine the data collection tools and to assess the reaction of the respondents to our research procedure. We had to take the socio-economic and general information, history of DR, investigation report of biochemical, anthropometrical and clinical measurements from the medical records and recheck these variables with the patients’ guide book. We also examined the biochemical parameters, measured anthropometrica and clinical parameters, and dietary history and physical exercise from the subjects at the level of 15 years. Thereby, we tested the construct validity of the questionnaire in this study.

5.2.1.2 Biochemical, clinical and anthropometric measurement
Biochemical parameters were measured by the technicians who are highly experienced in their fields and all laboratory analysis were performed in the BIRDEM laboratory facilities which has the highest credibility within the country. Blood pressure was measured by a physician on the right arm using normal cuffs for adult fitted with a standard mercury sphygmomanometer. The machine was checked everyday before starting the measurement. All anthropometrical measurements including height, weight, waste and hip circumference were measured by trained health workers (nutritionist) and standardized by measuring her own weight everyday morning and checked after every 20 patients.

5.2.1.3 Eye examination
The grading of retinopathy was carried out by an experienced ophthalmologist who specializes in diabetes and who has over 20 years experience in the assessment and management of retinopathy in this hospital. Visual acuity of each eye was tested separately by using Snellen’s distance vision chart at 6 metersS slit lamp examination was performed to document any abnormality in the anterior segment. Intraocular pressure was also measured using a schiotz tonometer before dilating the pupils and fundus photography was also taken to confirm the diagnosis as required.
5.2.2 Limitations of the study

5.2.2.1 Confounding effects
In a historical cohort study a researcher usually attempts to relate an exposure to an outcome but often measures an effect of third variable termed as confounding variable.

Waist and hip circumference
Although we were measured the waist and hip circumference of these study subjects at 15 years but it was not recorded in 5 and 10 years. Increased waist and hip circumference might have an association on development of DR, as the risk of DR in relatively overweight and obese patients in our study might have confounded by increased waist and hip circumference.

Diet and Physical activity level (PAL)
Diet and PAL in this study might have taken place from other associated phenomenon. But we did no have the follow-up history of these variables in first 5 and 10 years. It can be assumed that diet and PAL could have been confounded to increase the risk of DR among diabetic patients. Despite the fact, we did not postulate the association between PAL and diet with DR in this follow-up study because we did not have the record of dietary history and PAL in 5 and 10 years.

In multivariate analysis mathematical modeling has measured a potential effect of one variable while simultaneously controlling for the effect of many other variables. Therefore, this study was able to show independent factors for risk of DR by controlling the confounding effects of some other variables.

5.2.2.2 Biases
Selection bias
We acknowledge that hospital population had put potential limitations on the selection of samples. It is noteworthy that any hospital based study does have inherent selectiveness for its population group. However the results can be represented of the diabetic patients in Bangladesh since BIRDEM is a tertiary hospital covering diabetes care for whole of
Bangladesh. On the other hand, selection bias was not a major concern in this study because of the high response rate from both men and women.

**Recall and information bias**
Retrospective way of data collection in a historical cohort study may create some biases from recall problems. In some aspects the 24 hr dietary history was not recalled very correctly in this study. In addition, information bias can arise from the standpoint of local cultural context. In the answer regarding socio-economic status we encountered quite a lot of unknown answers. This might have arisen from the local cultural phenomenon where patient especially women feel ashamed of telling about their socio-economic status as well as their dietary pattern.

**5.2.2.3 Internal validity of the findings**
The history of diseases represented based on the hospital record and patient’s guide book in this study. We acknowledge that this might have impact on internal validity. Beyond this assumption as BIRDEM is the best service provider for diabetes care service the finding of the study obtains reliable data.

**5.2.2.4 External validity for generalization**
In terms of generalizability or external validity the findings of the study reflected the scenario of urban or semi-urban diabetic patients. The rural picture might have different from this population. However, we believe the findings of the study can be inferred on the general population and is more likely to be externally valid for the diabetic patients of Bangladesh.
5.3 Discussion on the findings of the study

5.3.1 Incidence of DR

DR is the most important ocular complication, which can lead to visual disability. Its incidence is rapidly increasing with increasing incidence of diabetes. There has been no substantive report on the incidence of diabetic retinopathy using longitudinal data from newly diagnosed type 2 diabetic patients. The DCCT study (63) reported data only from type 1 diabetes patients and the Wisconsin study reported on a mixed group of newly diagnosed and previously diagnosed patients on insulin (64). Data on the incidence and prevalence of DR are relatively rare in developing countries and those are almost absent in Bangladeshi population.

The present data was shown a high incidence of DR at 5 years after diagnosis of DM in compared to 10 and 15 years. This may have been due to the fact that many patients were already diabetic for several years when first detected in BIRDEM, but they were unaware about it. The study showed that the rising trend of the incidence of DR at 15 years was higher (similar to 5 years) compared to 10 years. This may indicate that duration of diabetes, lack of physical activity, and or other risk factors influenced for higher incidence at 15 years after diagnosis. It has been demonstrated that for every 5 year increase in the duration of diabetes the risk for DR increases by 1.89 times (65).

In the present study the frequency rate of DR has been found to be 11.8% at first 5 years and it was almost double in 10 to 15 years. Severity of DR increased with the duration of diabetes and most of the moderate to severe NPDR cases were identified at 15 years after diagnosis. In the CURES Eye study (65), 41.8 per cent had DR after 15 yr of diabetes and the severity of DR proportionally increased with longer duration of diabetes. Severe retinopathy (NPDR/PDR) however was more frequent in European type 2 than type 1 diabetic patient (66).

The incidence of DR increased with increasing age and duration. We have observed that at 5, 10 and 15 years the incidence of DR increased with increasing age and duration of diabetes. Particularly it was higher in the age group >60 years. Between 2000 and 2030,
the number of people in Asia who are older than 65 years is expected to increase by 168%. The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. In the study conducted by Dandona et al (67) in type 2 diabetes, it is reported that 87.5 per cent of those with >15 yr duration of diabetes had DR compared with 18.9 per cent of those who had <15 yr duration.

A higher incidence of DR among females compared to males, in all age categories has been noted; however, the difference was not statistically significant. This may reflect the fact that female has a significant contribution among study subjects and the level of physical activity are much more lower, the pattern of work is totally different and seating based, rapid urbanization, modified dietary pattern were the cause as such problem.

5.3.2 Risk factors for DR
Our data suggest that glycaemic control, measured either by FBG or 2 hr-ABF and HbA1C were the strongest risk factors for 5, 10 and 15 years of incidental cases of diabetic retinopathy controlling for potential confounding factors. In addition, among lipids TG, TC and higher blood pressure were found to be significantly independent risk factors for the development of DR. Obesity measure like BMI were not found to be associated with the incidental case of DR.

There is strong evidence to suggest that the development and progression of DR is influenced by the level of hyperglycemia (65, 68, 69). Univariate model showed that high levels of FBG, 2-hr ABF and HbA1c were found to be significantly associated with DR in 15 year follow-ups and the mean values of these variables were also significantly high in patients with DR compared to NDR. Conversely a similar increasing trend was found in multivariate model and the risk of DR was about 8.34, 3.45 and almost 5 times significantly higher in high levels compared to normal levels of HbA1c in this 15 years follow-ups. It was observed in another study that glycosylated hemoglobin levels, was a significant risk factor for the long-term progression of diabetic retinopathy (70). In contrast to our findings, European population with retinopathy had worse glycemic control than patients without retinopathy in ten years after diagnosis (66).
In our study univariate model showed high levels of TG in 15 year follow-ups and TC in 10 years appeared to be significantly associated with DR while LDL and HDL-C were not associated with it. It was also found that the mean value of TG, TC and LDL-C concentrations were higher in DR compared to NDR. Similarly a study have revealed that there was a significant association of serum triglycerides with DR and the mean serum cholesterol, serum triglycerides and HDL-C concentrations were higher in subjects with DR compared with those without DR (71). In this study serum lipids were not associated with DR in multivariate model. Several investigators have reported on the association of lipids with DR, but the results have not been consistent.

We have found the mean values of the systolic and diastolic hypertension were significantly higher among the DR compared to NDR patients. Previous study in Nepal showed that the development of diabetic retinopathy was twice more likely in hypertensive than non-hypertensive cases (54). Oman and Japanese population studies demonstrated that hypertension had a strong association with DR (72, 73). It was also noted in univariate model that the association between systolic and diastolic hypertension with DR were significantly higher in 15 year follow-ups excepting diastolic hypertension were not associated with it in 10 years. In contrast multivariate model showed systolic hypertension were significantly associated in first 5 year (p<0.05) and when it was adjusted for age in 15 years the association was more statistically significant (p<0.00).

In this study it is important to point out that there was a significant trend with increasing level of serum creatinine in patients with DR compared to NDR. It was also noted in univariate and multivariate model that the higher level of serum creatinine was significantly associated with DR at 10 and 15 years. This might have been due to progressive loss of excretory kidney function.

In univariate and multivariate model we found significant association with age and DR. When age was increased by 1 year the risk was 7.2% and 2.5% higher in 5 and 10 year (univariate model) and 6% higher (multivariate model) in first 5 years. Some studies have shown that older age with DM is a risk factor for the presence of DR (74, 75).
We did not find significant association with gender, education, the income level with DR. On the other hand the risk of DR was higher in the middle income group at the level of 10 and 15 years compared to the poor and high income groups.

As in other study (76), our univariate and multivariate analysis indicated that the residence of urban (P<0.00 in univariate model) and semi-urban (P<0.05 in multivariate model) population were significantly associated with DR in 10 years.

Earlier studies have shown that persons currently employed or working had fewer or no diabetic complications, as compared to those not working (77). Similar trend was noted with regard to employment/work in our study that employed or working persons had significant protective effect compared to unemployed at first 5 years in univariate and multivariate model. This may have occurred unemployed people to ignore these complications.

In our study we did not find any association with BMI for the risk of DR but the risk of DR was notably higher for the over weight and obese individuals but significant association was not found because of fewer subjects belonging in this groups. This may suggest that the present cut-off values for BMI may not be applicable for our population as to indicate the people at risk.

We did not observe any association between PAL and diet in this study. Therefore, we did not assume the association between PAL and DR in this follow-up study because we did not have the record for dietary history and PAL in 5 and 10 years.
Chapter 6

Overall Conclusion, Recommendation

&

Implementation Plan
6. Overall Conclusion, Recommendation and Implementation Plan

6.1 Conclusions

This is one of the first cohort studies of DR in Bangladesh over 15 years. The study showed a relatively high incidence of DR in this population. The incidence of DR increased with increasing of age and duration of diabetes. Higher rate of DR and NPDR were identified after 15 years of diagnosis. A higher incidence of DR was also observed among females in all age categories compared to males. This, along with aging of the population, may increase the predisposition to visual impairment due to DR in Bangladesh. Therefore, tight glucose controls are required to avoid retinal complication, for which improved coordination between physician and ophthalmologist are needed along with necessary policy developments. Timely laser photocoagulation therapy can also prevent loss of vision in a large proportion of patients with severe NPDR and PDR and/or macular edema. A significant number of patients with vision-threatening disease may not have symptoms; therefore, ongoing evaluation and strategy for retinopathy are required. Furthermore, in order to monitor the relative public health importance of visual impairment due to DR, new reliable population based data will be needed in the future.

The occurrences of associated risk factors for DR were identified at the follow-up in the end of 2008. Patients with retinopathy were found to have poor glycemic control, higher rate of lipid abnormalities, the presence of nephropathy and hypertension during three different time periods of observation compared to patients without retinopathy. Contradictory to the established risk factor for obesity measures like BMI were not found as a significant risk factor for the development of DR in this population. This may call for re-examination for BMI categories for our population in order to identify the people at risk for the development of DR. For this follow-up study we could not confirm the association of DR with diet and PAL due to missing data. Therefore, further research is recommended to identify the relationship between diet and PAL with DR. Further educated counseling is possibly required for the modification of lifestyle including physical activity and thereby improved glycemic control.
The significant associations with poor diabetes control are consistent with the hypothesis that the metabolic derangements of diabetes are a major cause of retinopathy. In addition, our findings suggest that hypertension and the presence of nephropathy were significantly associated with the development of DR in type 2 diabetic patients. Treatment modalities exist that can prevent or delay the onset of diabetic retinopathy, as well as prevent loss of vision, in a large proportion of patients with diabetes. The DCCT and the UKPDS established that glycemic and blood pressure control can prevent and delay the progression of diabetic retinopathy in patients with diabetes. Our data also support that controlling blood glucose and blood pressure levels can delay the development of retinopathy or slow its progression. People with diabetes should work closely with their health care team for improvement outcomes. Based on the findings from this study and future population dynamics, it is imperative that eye care service delivery be organized in coordination with diabetes care.
6.2 Recommendations

1. Patients with diabetes mellitus should be invited to attend for the DR screening test.

2. Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after diabetes diagnosis.

3. Patients with type 2 diabetes should be ensured photographs are of adequate quality and grading is accurate by an ophthalmologist.

4. Eye examinations for both type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Examinations will be required more frequently if retinopathy is progressing.

5. Patients with any level of macular edema, severe NPDR, or any PDR require the prompt care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. Referral to an ophthalmologist should not be delayed until PDR has developed in patients who are known to have severe nonproliferative or more advanced retinopathy.

6. When planning pregnancy, women with preexisting diabetes should have a comprehensive eye examination and should be counseled on the risk of development and/or progression of diabetic retinopathy.

7. Patients with diabetes mellitus without diabetic retinopathy should be encouraged to have annual dilated eye examinations to detect the onset of diabetic retinopathy.
6.3 Implementation Plan

The Implementation Plan represents the current understanding of what needs to be done, by whom and by when to deliver towards the best, together. Our study focused that among type 2 diabetic patients the total number of DR increased from the 1993 to the 2008 cohort at 15 years of follow-up. To reduce the new visual impairment due to retinopathy:

1. We suggest carrying out a screening program preferably at the time of diagnosis, regular follow-up together with good metabolic control to prevent the sight-threatening diabetic retinopathy.

2. We recommend motivating the patients to visit the clinic on a regular schedule and for doctors to educate patients with DR about the importance of follow-up visits in managing this complication of diabetes effectively.

3. A slightly higher incidence of DR among females was found in our study. Therefore, women should be counseled and inspired by a physician or skilled healthcare personnel to prevent diabetic retinopathy through optimal treatment of blood sugar and blood pressure and physical activity levels.

4. We also propose carrying out a patient education program about the importance of maintaining near-normal glucose levels and near-normal blood pressure and lowering serum lipid levels and modify lifestyle that leads to obesity for diabetic retinopathy, despite good vision and no ocular symptoms.

5. We would suggest for conducting a training program for health professionals to handle these patients by friendly manner.

6. Factors associated with DR were similar to other developed countries. To prevent this condition of DR, the coordination between physician and ophthalmologist should be needed strengthen.
7. Our study could not demonstrate on the association of diet and PAL with DR due to missing data in this 15 year follow-ups. Consequently, an additional study needs to be taken up to measure the association of these factors with DR in Bangladesh.

8. We would also suggest for conducting a population-based surveillance study for the incidence of and factors associated with DR in the Bangladeshi diabetic population.

9. Further an intervention study on this issue would have long term implication of DR on the promotion of health and reduction of disease burden. Subsequently the effects of these interventions on risk factors and the target outcome should be monitored, and their impact and cost-effectiveness should be evaluated.
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PAPER I
Paper I

Incidence of Diabetic Retinopathy amongst type 2 diabetic patients in Bangladesh -a hospital based study

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**OBJECTIVE**- To investigate the 5, 10 and 15 years of incidence rate of diabetic retinopathy in Bangladeshi type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS**- A random sample of 977 diabetic patients were recruited in 2008 amongst those who were primarily diagnosed in 1993 for the first time in the out patient department, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM). Diabetic Retinopathy was graded using the Early Treatment Diabetic Retinopathy Study. All patients were examined by an ophthalmologist and were reconfirmed by a senior ophthalmologist.

**RESULTS**- Of the 977 subjects investigated, 468 were male and 509 were female (mean±SD, age 56±8 years). The incidence rates of DR per 1000 person years were 23.54 (95% CI 19.61-28.26), 17.52 (95% CI 14.93-20.55) and 21.47 (95% CI 18.86-24.44) at 5, 10 and 15 years respectively. Incidence of DR increased with increasing age, but this was more prominent in female subjects. Non Proliferative DR (NPDR) was found in 115 patients (11.8%) at 5 years, while this was 13.9% at 10 years and 11.4% at 15 years of follow-ups. Severity of DR increased with the duration of diabetes. Most of the moderate to severe NPDR cases were identified at 15 years control.

**CONCLUSIONS**- Higher rate of DR and NPDR were observed in this population. The severity of the condition intensified with the duration of diabetes. Therefore, necessary strategies are needed to cope with the increasing challenge of diabetes epidemics in Asian subjects. Furthermore, tight glucose controls to avoid complication are warranted, for which improved coordination between physician and ophthalmologist are needed along with necessary policy developments.

**Key words**- Type 2 diabetes, Incidence, Diabetic retinopathy.
INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (1). It is now an emerging epidemic worldwide, and it is estimated that globally there are now 246 million people with diabetes, and that this number will rise to 300 million by 2025 (2). The prevalence is increasing in both developed and developing countries, but most of which will occur in Asia (3). The World Health Organization (WHO) Report on diabetes prevalence alarmed that diabetes has posed a serious threat to developing countries with respect to their existing health care services (4). Formerly described as a ‘disease of affluence’, it has now become evident that, owing to demographic changes, cultural transition and population ageing, diabetes is also now translated as a disease of the developing countries (5). Recent epidemiological studies have shown an increased prevalence of diabetes in India (12.1%), Pakistan (11.1%), and China (6.1%) (6-8). Estimated number of diabetics for the South East Asia region is 38,488,650 (9). Bangladesh, with her 150 million people and per-capita income of US $270 per year is also facing a high prevalence of diabetes mellitus (DM) and the prevalence of DM is in urban 8.1% and 2.3% in rural areas (10). But over five years 1999-2004 the rural epidemics had experienced a 300% increase in prevalence (Ref-11).

The morbidity and mortality in DM are largely related to complications which are divided in two main groups: macrovascular complications and microvascular complications. The high disease burden reflects high rates of both micro and macro vascular complications from diabetes resulting in diminishing quality of life and productivity.

Diabetes is one of the most common leading causes of blindness in 20-74-year old persons (12). Diabetic eye complications and, in particular, diabetic retinopathy (DR) is one of the major micro vascular and possibly the initial complications of diabetes. DR is a chronic progressive sight-threatening disease of the retinal microvasculature associated with the prolonged hyperglycaemia and other conditions linked to diabetes mellitus such as hypertension (13). WHO estimates at present that DR is responsible for the blindness of 4.8 million people in the world. Projections based on the increased life expectancy,
changes in lifestyle, decreased incidence of communicable diseases with superimposed genetic and environmental factors, it is presumed that if there is no timely intervention, a further rise is expected both for diabetes and its complications. Reducing the impact of retinopathy is highly desirable from clinical to both a social and economic perspective.

Data on diabetic retinopathy is largely unknown in Bangladesh. Even in the region incidence data on DR is scare. Previous studies have indicated differential risk factors for both the occurrence and its complications of diabetes. Therefore, incidence data of DR from Asian Indian subjects, where the highest rise of diabetes is expected to occur are warranted from the global perspective but also for the development of national strategies both for improved clinical service and its occurrence in the first place. We have conducted a retrospective cohort study over 15 years including 977 subjects in order to observe the 5 year, 10 year and 15 years of incidence rate of diabetic retinopathy in Bangladeshi type 2 diabetic patients.
MATERIALS AND METHODS

Subjects and setting

A hospital-based, historical cohort study was designed. A group of 977 Bangladeshi type 2 diabetic subjects, aged 30 years and above, who were first diagnosed and then regularly followed in the Outpatient Department of BIRDEM during 1993 to 2008, were recruited randomly for this study. The study design is outlined in Figure 1.

Figure 1: Flow Chart of Patient recruitment and follow-up.
**Data Collection Procedures**

**Hospital Registry and Diabetic guide book**

Data were collected from the hospital registry and patients’ diabetic guide book. Socio-demographic, anthropometric, medical history, clinical and laboratory findings and treatment on diabetes are recorded systematically in the diabetic guide book developed by Diabetic Association of Bangladesh. A detailed history of disease onset and the illness were taken from this patient’s diabetic guide book.

**Type of diabetes**

The classification and diagnosis of diabetes was made by the reporting physician according to the World Health Organization (WHO) criteria (1). Diagnosis of diabetes was made in each case by a standard oral GTT with 75gm glucose load for type 2 diabetes.

**Eye Examination Method**

The ophthalmologic examination included best corrected visual acuity (14), slit-lamp biomicroscopy, applanation tonometry and also detailed fundus examination (15) by both indirect ophthalmoscopy and contact lens biomicroscopy (with pupils dilated) conducted by retinal specialist. All patients were examined by an ophthalmologist and were reconfirmed by a senior ophthalmologist. After complete eye examination, the necessary treatment was provided.

The grading of retinopathy was defined and classified (16) into the most commonly used clinical classification today is the modified Airlie House classification as was introduced by ETDRS: Non-Proliferative Diabetic Retinopathy (NPDR) or background retinopathy:- NPDR was classified into: ‘mild’, ‘moderate’, ‘severe’ and ‘very severe’. Proliferative Diabetic Retinopathy (PDR):- PDR was classified into: ‘early PDR’, ‘PDR with high risk criteria’, ‘PDR including advanced diabetic eye disease’. The ETDRS classified diabetic macular edema as non-clinically significant and clinically significant (CSME) (17).
Data analysis and statistical methods
Data were first compiled through a custom made software developed by the Information Management Unit of the Hospital. Those were edited, classified and coded on same day for completeness and accuracy of the data. Data were then imported into SPSS version 12.0 (Statistical Package for Social Science), by IT department in Bangladesh. Descriptive statistics were presented using frequency table and cross tabulations. The formula (18) was used to estimate stratified incidence rate per 1000 person-years and 95% confidence intervals. For time consuming the formula was put into SPSS 16.0 using syntax to perform the calculation.

Ethical consideration
Ethical clearance was obtained from the Ethical Review Committee (ERC) in Norway and from the Diabetic Association of Bangladesh (DAB) before commencement of the study. Ethical guidelines of Declaration of Helsinki IV (2001) were followed throughout the study. All patient records in BIRDEM are preserved and unauthorized accesses to these records are prohibited. Since the patient data was used in this study, the subjects’ personal information was kept confidential. There was no possibility of harming the patients or the institute by the analysis of these recorded data. Informed written consent was taken at the time of enrolling the patients. The rationale and objective of the project was written in plain and simple Bengali language and each patient was briefed about the benefits and risks of the project. All patients were informed that they were free to leave or to refuse to take part in the research at any time. Each patient was given a separate identify number. No undue incentive was given to the patient.
RESULT

Of the 977 newly diagnosed type 2 diabetic patients included in the study, 468 were male and 509 were female and about 63% were in age category between 45-60 years (Table 1). Among the study subjects 93% was Muslim and 80% came from urban areas, 50% belonged to middle income group and more than 60% of the participants had undergraduate level (1-12 years) of education.

Incidence of DR increased with increasing age at 5, 10 and 15 years for both gender but only small variation of incidence was observed over time. There was a marked decrease in incidence of DR from 5 years to 10 years and increased to a comparable level of 5 years incidence at 15 years assessment (Table 2).

Total number of DR after diagnosis increased from the 1993 to the 2008 cohort at 15 years of follow-up. The occurrence rate of DR was 11.8%, 17.5% and 32.2% at 5, 10 and 15 years respectively. With the duration of diabetes, proportion of NPDR cases was largely unchanged while the severity of NPDR increased with time. At 15 years of follow-up, eye changes were more pronounced (Table 3).
DISCUSSION

We found a relatively high incidence of DR in this population. DR was more prominent with the age of the subjects rather than the duration of diabetes. The study showed a high incidence of DR at 5 years (23.54; 95% CI, 19.61-28.26) and relatively lower incidence at 10 years and an increased incidence at 15 years after diagnosis. This may indicate late diagnosis at first time and therefore suffered from uncontrolled hyper glycaemia for an unknown period of time prior to diagnosis. Therefore, at 10 years we observe a dwindling incidence while it increased again at 15 years, possibly owing to the duration of DM and also a possible impact of age related lesser physical activity. Diabetic Retinopathy is known to be influenced with the duration of DM (19, 20, 21). The Wisconsin study showed that the four-year incidence of any retinopathy who were not using insulin at the baseline was 34.4% (95% confidence interval 29.2, 39.6) (22).

Severity of DR increased with the duration of diabetes and most of the moderate to severe NPDR cases were identified at 15 years after diagnosis. In contrast to our findings, most of the diabetic retinopathy was of the mild or moderate NPDR and PDR type in India (19) as well as European population in ten years after diagnosis (23). The prevalence of more severe grades of retinopathy was higher in Pima Indians with longer durations of diabetes (24). Both in T1DM and T2DM the presence and the severity of DR were increasing as the duration of DM increases (11). Severe retinopathy (NPDR/PDR) however was more frequent in type 2 than type 1 diabetic patient has shown in European study (23). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the rate of PDR varied from 2% in patients who had DM for less than 5 years to 15.5% in diabetics who had DM for 15 or more years (25). Furthermore, previous study has demonstrated that for every five year increase in duration of diabetes, the risk for DR increased by 1.89 times (20).

In our study, the frequency rate of DR was 11.8% at first 5 years and increased to 32.2% at fifteen years. In the CURES Eye study (20), 41.8 per cent had DR after 15 yr of diabetes and severity of DR proportionally increased with longer duration of diabetes.
The UKPDS (26) showed that over 6 years from diagnosis of type 2 diabetic, 22% had developed retinopathy.

The incidence of DR increased with increasing age and duration. We have observed that at 5, 10 and 15 years the incidence of DR was increased with increasing age and duration of diabetes. Particularly it was higher in the age group >60 years. Between 2000 and 2030, the number of people in Asia who are older than 65 years is expected to increase by 168% (3), even if rates are lower, the actual need for services for this group may be greater. The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. In the study conducted by Dandona et al (19) in type 2 diabetes, it is reported that 87.5 per cent of those with >15 yr duration of diabetes had DR compared with 18.9 per cent of those who had <15 yr duration.

To the best of our knowledge, there have been few or no substantive reports on incidence of diabetic retinopathy using longitudinal data from the developing nations. Although the DCCT study (27) reported data from type 1 diabetes patients and the Wisconsin study reported on a mixed group of newly diagnosed and previously diagnosed patients on insulin (28). Different types of study on diabetic retinopathy are well explored in the developed but almost absent in the developing countries especially follow-up studies.

Further we have found in our study that a higher incidence of DR among females in all age categories compared to males. This may indicate that female subjects may have been exposed to higher rate of uncontrolled hyperglycaemia due to treatment preferences and restricted physical activity. This finding is similar to the Japanese type 2 diabetic patients study (29). In the Wisconsin study, men had a slightly higher rate of retinopathy progression during 10 years (28). Cultural practice for treatment by gender may have played a major role rather than being female as a gender.

The strengths of our study are that it is 15 years retrospective follow-up study based on large sample size and the grading of retinopathy was carried out by an experienced ophthalmologist who specializes in diabetes, who has over 20 years experience in the assessment and management of retinopathy. The drawback of the study is that, it is hospital-based; therefore, in order to monitor the relative public health importance of
visual impairment due to DR, new reliable population based data will be needed in the future. Notwithstanding this limitation, our hospital based findings may be useful in the future planning of eye diseases, especially in DR and this current 15 year follow up of this cohort will also provide the incidence data of DR in Bangladesh.

Acknowledgements
We acknowledge the contribution of our survey team members and the physicians for their sincere and enduring contribution to the collection of data. We also thank all the participants in the study for their active participation.
### Table 1: Baseline Characteristics of 977 Newly Diagnosed Type 2 Diabetic Patients

<table>
<thead>
<tr>
<th>Area of Living*</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>784 (80.2)</td>
</tr>
<tr>
<td>Semi-urban</td>
<td>57 (5.8)</td>
</tr>
<tr>
<td>Rural</td>
<td>136 (13.9)</td>
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</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total number (%)</th>
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</thead>
<tbody>
<tr>
<td>&lt;45 years</td>
<td>115 (11.8)</td>
</tr>
<tr>
<td>46-60 years</td>
<td>617 (63.2)</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>245 (25.1)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>468 (47.9)</td>
</tr>
<tr>
<td>Female</td>
<td>509 (52.1)</td>
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</table>

<table>
<thead>
<tr>
<th>Occupation**</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed</td>
<td>373 (38.2)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>604 (61.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Income Level***</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>236 (24.2)</td>
</tr>
<tr>
<td>Middle</td>
<td>507 (51.9)</td>
</tr>
<tr>
<td>High</td>
<td>234 (24.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Religion</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muslim</td>
<td>910 (93.1)</td>
</tr>
<tr>
<td>Others</td>
<td>67 (6.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education****</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illiterate</td>
<td>59 (6.0)</td>
</tr>
<tr>
<td>Under Graduate</td>
<td>619 (63.4)</td>
</tr>
<tr>
<td>Graduate and Above</td>
<td>299 (30.6)</td>
</tr>
</tbody>
</table>

*Area- Semi-urban: The mixture of single-family homes, asphalt, and greenery on the fringe of the city reflects a lower physical density;  
**Occupation-Employed: Self employed or government employees, Unemployed: Housewives and jobless;  
***Income level- Poor: <10,000, Middle: 10,000-20,000 and High: >20,000 BDT  
****Education- Illiterate: Unable to write & read, Under graduate: Having primary & higher education
Table 2: Incidence of DR with 95% CI by age and gender, Bangladesh

<table>
<thead>
<tr>
<th>Age in years</th>
<th>5 Years</th>
<th>10 Years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>DR</td>
<td>Incidence per 1000 PY (95% CI)</td>
</tr>
<tr>
<td>&lt; 45 Male</td>
<td>37</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 45 Female</td>
<td>78</td>
<td>1</td>
<td>2.56 (0.36-18.20)</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>1</td>
<td>1.74 (0.24-12.35)</td>
</tr>
<tr>
<td>45 – 60 Female</td>
<td>34</td>
<td>21</td>
<td>21.64 (15.68-29.86)</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>57</td>
<td>18.48 (14.25-23.95)</td>
</tr>
<tr>
<td>&gt;60 Male</td>
<td>15</td>
<td>35</td>
<td>44.87 (32.22-62.50)</td>
</tr>
<tr>
<td>60 Female</td>
<td>89</td>
<td>22</td>
<td>49.44 (32.55-75.08)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>57</td>
<td>46.53 (35.89-60.32)</td>
</tr>
</tbody>
</table>

DR = Diabetic Retinopathy, py= person year, CI= Confidence Interval  
n= Number of patients
<table>
<thead>
<tr>
<th>Stages of Diabetic Retinopathy</th>
<th>Total number in Year 5 (%) (n=977)</th>
<th>Total number in Year 10 (%) (n=862)</th>
<th>Total number in Year 15 (%) (n=711)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>115 (11.8)</td>
<td>136 (13.9)</td>
<td>111 (11.4)</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>14 (1.4)</td>
<td>77 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>1 (0.1)</td>
<td>33 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Very severe NPDR</td>
<td></td>
<td>5 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Early PDR</td>
<td></td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Total Number (%)</td>
<td>115 (11.8)</td>
<td>151 (17.5)</td>
<td>229 (32.2)</td>
</tr>
</tbody>
</table>
References


PAPER II
Paper II

Risk factors for Diabetic Retinopathy among Bangladeshi diabetics
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OBJECTIVE- To identify the risk factors for developing diabetic retinopathy (DR) and to examine its association with socio-demographic, anthropometric, clinical, nutritional, biochemical parameters and DR among Bangladeshi type 2 diabetic patients.

RESEARCH DESIGN AND METHOD- About twelve hundred newly diagnosed type 2 diabetic subjects registered at BIRDEM Hospital (the tertiary hospital of the Diabetic Association of Bangladesh), OPD since 1993 to 2008 were randomly selected in this follow-up study. Among them nine hundred seventy seven patients were included for this study who was free of any ocular complains in both eyes. Diabetic Retinopathy was diagnosed by a qualified Ophthalmologist and it was graded following the Early Treatment Diabetic Retinopathy Study. Diabetic Retinopathy (DR) was diagnosed by retinal color photography and classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS). Relevant clinical information including age, duration, blood glucose estimation, lipid profile, HbA1c levels, serum creatinine levels and hypertension were also obtained. Univariate and multivariate generalized linear models were used to assess associations of clinical, biochemical and anthropometric variables with retinopathy. Relative risks with 95% confidence intervals were used to assess association between the variables.

RESULTS- Patients with retinopathy had worse glycemic control during three different time periods than patients without retinopathy (HbA1c 9.6±2.6 vs 7.7±2.3%, 9.9±2.1 vs 8.0±2.3% and 10.38±2.1 vs 7.27±1.5%, respectively; P<0.05). It was found that age, area of residence, occupation, poor diabetes control (FBG & 2-hr ABF), total cholesterol, triglycerides, the serum creatinine level and hypertension were significantly associated for the development of retinopathy in 15 year follow-ups. In the multivariate analysis increasing age, FBG, A1C, TG, SBP were important independent risk factors for the development of DR. Higher level of serum creatinine and DBP were found to have significantly contributed for DR at 10, 15 years and 5, 15 years respectively. Nutrient intake and BMI appeared to have played a non-significant role as a risk for the development of DR possibly because the population in general relatively lean (mean±SD, 24.3±3.0).
CONCLUSION- Duration of diabetes has a straightforward relation with DR and glycemic control is the prime significant risk factor for the development of retinopathy at 15 years of follow-up. Other potentially risk factors may be important, including elevated blood pressure, TG and the presence of nephropathy.

Key words- Type 2 diabetes, Risk Factors, Diabetic Retinopathy.
INTRODUCTION
Diabetic retinopathy is a common complication of diabetes and despite the availability of effective treatment; it remains one of the leading causes of visual loss (1–3). It is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment (4). The longer patients have diabetes, the higher the prevalence of DR (5). According to the World Health Organization, approximately 5 million individuals have diabetic retinopathy, accounting for 5 percent of world blindness. By 2025, an estimated 300 million people will have diabetes, with half expected to develop some level of retinopathy. In developed countries, DR is recognized as the leading cause of blindness in the working-age population (20–74 years old) and is responsible for 12% of new cases of blindness each year (6). With the rate of DR increasing not only in developed countries, but in underdeveloped countries, it poses an enormous public eye health challenge and financial burden. The rapid increase in the number of persons with diabetes is expected to lead to an increase in the number of persons with complications from diabetes. Diabetics have 29 times higher chance of becoming blind due to DR than non-diabetics of the similar gender and age (7).

Several factors have consistently been identified by epidemiological studies as risk factors in the development of diabetic retinopathy: duration of diabetes, systolic blood pressure (SBP), glycemic control, and urinary albumin (8, 9). Other factors, including BMI, smoking, serum lipids, and C-peptide, have shown varying results (9-11). It is now known that duration of diabetes and degree of hyperglycemia have a central role in DR, but maintenance of normoglycemia does not always completely prevent the development of the DR. Thus, additional factors related to the diabetic state are postulated to have a causal role in this disorder.

There are several proposed pathological mechanisms by which diabetes may lead to development of retinopathy. Although many of the risk factors of DR have new been identified there are still confusion regarding the precise role of these factors and, consequently, regarding the pathophysiology of the disorder.
In Asia, many cross-sectional studies have been done on the prevalence as well as the associated risk factor for developing DR. However, relatively few studies have investigated the causal factors underlying DR in Asians. This is due to the lack of prospective studies without which it is extremely difficult to establish the causation of DR. Large-scale studies to identify the extent of the problem and its associated risk factors are almost absent in Bangladesh. The present study was designed to investigate the relative association of baseline socio-demographic, anthropometric, clinical, nutritional and biochemical parameters with development of DR in Bangladeshi type 2 diabetic patients under a 15 years follow up.

**Materials and Methods**

**Subjects**

This study was a hospital-based historical cohort of newly diagnosed type 2 diabetic subjects (both male and female, aged ≥ 30 years) registered in the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM) since 1993 to 2008. Among the 1198 patients first selected- 101 were already dead, 87 could not be located, 37 refused and 977 were included for analyses. All of these 977 patients were free from DR in both eyes at baseline (1993). The patients were then grouped into DR and non-DR groups during the follow up period.

**Study hospital BIRDEM**

The place of study was BIRDEM (the central institute of Diabetic Association of Bangladesh) which runs one of the largest diabetes out-patient clinic in the world (around 3000 patients per day). Availability of a large number of DR patients in its Ophthalmology OPD was the main reason for choosing this hospital. Being a charity the hospital attracts patients with diverse demographic and socioeconomic background from all over the country. Thus, data generated from this hospital may reflect the trend in the general population.
Ethics
Informed written consent was taken from each of the individuals prior to inclusion. Self
decision of patients to participate or not in the research was properly honored by the
Team. The protocol was approved by the relevant Norwegian and Bangladeshi Ethical
Committees.

Survey procedures
Three days training (both theoretical and practical) for the health workers were
conducted prior to the beginning of the study. A structured questionnaire was developed
and translated into Bengali language and revised after pre-testing. Those patients who
could not read had the questions read out to them by one investigator. Fasting blood
glucose, biophysical examination and socio-demographic information was also collected
for the chosen 977 patients during the month of August-November 2008.

Hospital Registry and Diabetic guide book
Data were collected from the hospital registry and patients’ guide books. Socio-
demographic, anthropometric, medical history, clinical and laboratory findings and
treatment on diabetes are systematically recorded in these guide books developed by the
Diabetic Association of Bangladesh. A detailed history on the onset of disease were
taken from these books.

Eye Examination Methods
The ophthalmologic examination included best corrected visual acuity (12), slit-lamp
biomicroscopy, applanation tonometry and also detailed fundus examination (13) by both
indirect ophthalmoscopy and contact lens biomicroscopy (with pupils dilated) conducted
by a retinal specialist. The grading of retinopathy was defined according to the modified
Airlie House classification adopted by the Early Treatment Diabetic Retinopathy Study
(14). All patients were examined by an ophthalmologist and were reconfirmed by a
senior ophthalmologist.
**Anthropometric measurements**

Anthropometric measurements such as weight, height, waist and hip circumferences were taken from the patients wearing light clothes and without shoes. The weight was measured to the nearest 0.1 kg using a Sohenle mechanical weighing scale and the machine was calibrated daily by known standard weight. Height was taken to the nearest 0.5 cm using a portable, locally manufactured stadiometer with subjects standing upright on a flat surface without shoes having the back of the heels and the occiput on the stadiometer. Waist circumferences was measured by placing a plastic dressmaker’s tape horizontally midway between the lower border of the ribs and the iliac crest on the mild-axillary line. The measurement was recorded to the nearest centimetre. Hip circumference was measured to the nearest centimetre at the greatest protrusion of the buttocks just below the iliac crest. Waist hip ratio was taken as waist/hip circumference. Body Mass Index (BMI) was calculated as the ratio of weight in kilograms over height in meters squared \[\text{weight (kg)/height (m}^2\text{)}\]. The definition of overweight and obesity was based on BMI $\geq 25$ kg/m$^2$ and $\geq 30$ kg/m$^2$ respectively. (15).

**Measurement of blood pressure**

Three readings of blood pressure, at 10 minutes interval, were taken from each participant. Measurements was taken on participants on a sitting position after 5 minutes rest, by trained and certified health workers following AHA procedures, using electronic AND 078 Model UA-767 fully automatic, clinically validated digital BP monitor, with a suitable sized cuff (Small 9x18 cm, medium 12x23 cm and large 15x33 cm) at the forearm. Hypertension was deemed to be present when the systolic pressure was greater than 140 mmHg or when the diastolic pressure was greater than 90 mmHg (16).

**History of dietary intake and energy expenditure**

Using 24 hr-recall method the dietary history of the subjects were collected. In the 24 hr-recall method the subjects are asked by the health workers to recall the subject’s exact food intake during the previous twenty-four-hour period. Food list album and the food stuff (plate, glass, spoon) were also used for this dietary history. Energy expenditure of the subjects was also recorded in this study. It was calculated by factorial method ((WHO/FAO/UNU 1985).
**Biochemical measurements**

Venous samples after overnight fasting of at least 8 h were collected in ethylenediamine tetraacetic acid (EDTA) tubes and centrifuged. Plasma glucose was estimated by a glucose oxidase method. Fasting plasma glucose ≥7 mmol/L, 2-hr ABF ≥11.1 mmol/L (16) and Hemoglobin A1c >7% were considered as a type 2 diabetic patients in this study. Lipid abnormalities were deemed to be present when the TC was >200 mg/dl, TG was >150 mg/dl, LDL was >100 mg/dl, HDL was <40mg/dl for men and <50 mg/dl for women (Ref-20). The presence of nephropathy was considered when the serum creatinine level was >1.5 mg/dl (17).

**Statistical analysis**

Student’s t test was performed to compare with DR (Diabetic Retinopathy) and NDR (No Diabetic Retinopathy). Univariate and multivariate generalized linear models were used to assess associations of clinical, biochemical and anthropometric variables with retinopathy. The associations were presented in form of relative risks (RRs) and 95% Confidence Intervals (CIs). When the univariate analyses showed significant relationships (p < 0.25) between exposure variables and retinopathy, these exposure variables (risk factors) further were included into the multivariate analysis (final model). The p-values less than 0.05 were considered statistically significant. All p-values presented are two tailed. The data were analyzed using a computer program Statistical Package for Social Science (SPSS) (Windows version 16.0).
Results

The differences of mean values between DR and NDR patients from 1993 to 2008 cohort:

High levels of mean Fasting blood glucose, 2h. BG, HbA1c, Total cholesterol, TG, serum creatinine systolic and diastolic blood pressure in patients of diabetes with retinopathy compared to those without the condition (Table 1).

It was found that serum cholesterol in 10, 15 years (210.0±42.9 vs 198.7±43.0, 216.4±45.1 vs 204±40.5 mg/dl, respectively; P<0.05); serum triglycerides in 5 (199.4±88.5 vs 170.7±71.9 mg/dl, P<0.05), 15 years (200.0±86.4 vs 180.1±70.5 mg/dl, P<0.05) and LDL-cholesterol concentrations (137.8±43.4 vs 130±38.5 mg/dl, P<0.05) in 15 years were significantly higher in subjects with DR compared to NDR.

We have observed that systolic (130±12.3 vs 126±11, 129±11.7 vs 125±10.8 and 132±11.2 vs 123±9.1 mmHg, respectively; P<0.05) and diastolic blood pressure (84±8.31 vs 80±7.5, 83±7.0 vs 81±7.6 and 85±6.0 vs 79±5.6 mmHg, respectively; P<0.05) was significantly higher in DR groups than NDR in 5, 10 and 15 year follow-ups respectively.

Serum creatinine was also found to be significantly higher in DR compared to NDR subjects at the level of 5, 10 and 15 years (1.15±0.35 vs 1.07±0.3, 1.36±0.44 vs 1.14±0.37 and 1.8±0.74 vs 1.11±0.42 mg/dl, respectively; P<0.05).

BMI, however, did not differ significantly between the groups at 15 year follow-up (Table 1).

In our study PAL and dietary intake (both macro and micro nutrient) did not differ significantly between the groups in 15 year follow-ups. Except the fiber intake was significantly lower (5.97±2.42 vs 6.50±2.52 g/day, P=0.008) in DR compared to NDR groups (Table 2). On the other hand, the mean vitamin A and vitamin C (mg/day) intake was slightly lower and higher in subjects with DR compared to NDR at the level of 15 years.
Identified risk factors:

In univariate analysis age was found to be significant association with DR in first 5 (P<0.00, RR= 1.072 in 95% CI: 1.05-1.09) and 10 years (RR= 1.025 in 95% CI: 1.00-1.04) after diagnosis (Table 3). But multivariate analysis showed that age was found to be significant association with DR in first 5 years (P<0.00, RR= 1.06 in 95% CI: 1.04-1.08) (Table 4).

Other socio-demographic factors, such as- sex, education and the level of income were not associated with DR in different three time periods. But in both univariate and multivariate analysis the risk of DR was noted higher in females compared to males. Protective effect was also found in the level of education (under and above graduate compared to illiterate) and the risk of DR was higher in the middle income group at the level of 10 and 15 years compared to the poor and high income groups (Table 3, 4).

The risk of DR was significantly higher in urban population (P<0.00, RR= 1.76 in 95% CI: 1.2-2.4) in univariate model at 10 years (Table 3) and in multivariate model the risk of DR was significantly higher in semi-urban population (P<0.05, RR= 1.83 in 95% CI: 1.0-3.1) at the level of 10 (Table 4). In Univariate and multivariate model, a significant protective effect was shown in the employed subjects compared to unemployed subjects at first 5 years (P<0.00, RR= 0.40 in 95% CI: 0.2-0.6 and P<0.05, RR= 0.59 in 95% CI: 0.3-0.9) (Table 3 & 4).

The patients having FBG ≥7 mmol/L, the risk for DR was almost 4, 3 and 5 times significantly higher than the patient had FBG<7 mmol/L and 2-hr ABF was shown 3.5, 3 and 6 times significantly higher who had ≥11.1 mmol/L compared to the normal level. On the other hand, HbA1C levels ≥7 (%) was also found 3.7, 8.3 and 7.4 times significantly higher for the development of DR during the study periods compared to those had <7 (%). In multivariate model we did not set together FBG and 2-hr ABF because biologically they were strongly correlated. The risk for DR was found to be significantly [3.2 (CI: 1.7-5.8), 2.55 (CI: 1.5-4.3) and 2.99 (CI: 1.9-4.7) times] higher who had FBG ≥7 mmol/L compared to the normal levels during the study periods. On the other hand, the higher levels of HbA1C in first 5 and 10 years (it was adjusted for age
because lesser number of subjects was completed this test in those years) were found to be 8.34 and 3.45 times and in 15 years almost 5 times (P<0.00, CI: 2.8-8.5) significantly higher for the development of DR compared to normal levels (Table 3A & 4).

At 5, 10 and 15 years after diagnosis serum triglycerides level those who had ≥150 mg/dl was significantly higher (P<0.01, RR= 1.56, 1.50 and 1.37 respectively) and patient had ≥200 mg/dl serum cholesterol was significantly higher (P<0.05, RR= 1.36 in 95% CI: 1.0-1.8) in 10 years compared to the normal level, while LDL and HDL-cholesterol were not statistically significant for the development of DR in univariate analysis. But in multivariate analysis, we did not observe any significant association with TC and TG for the development of DR. In this model we did not set LDL and HDL-C because they were strongly correlated with TC and TG (Table 3A & 4).

Persons with high levels of serum creatinine during the study periods were more likely to have progression of retinopathy than persons with normal levels. In univariate and multivariate analysis, who had the level ≥1.5 mg/dl it was found to be 3.15, 2.66 (P<0.00, CI: 2.3-4.1 and CI: 2.0-3.5) times higher in 10 years and 4.64, 4.67 times higher (p<0.00, CI: 3.7-5.6 and CI: 3.8-5.7) in 15 years compared to the normal levels (Table 3A & 4).

In 15 years serum creatinine and SBP was adjusted for age because very few subjects was in the level of <1.5 mg/dl (39%) and ≥140 mmHg (13%) groups. On the other hand, DBP did not set in this model with SBP because they were strongly correlated. Systolic blood pressure those who were not in normal range was found to be significantly associated with DR in different three time periods (RR= 2.19, 1.81 and 2.59 respectively) and patient had ≥90 mmHg diastolic blood pressure showed 3.43 and 2.03 (P<0.00, CI: 2.2-5.2 and 1.4-2.7) times higher risk for the development of DR in first 5 and 15 years follow-up (Table 3A). In contrast it was observed in multivariate analysis that hypertension was significant association with DR in first (P<0.05, RR= 1.67 in CI: 1.0-2.6) and 15 (P<0.00, RR= 2.63 in 2.1-3.2, adjusted for age) years after diagnosis (Table 4).
In univariate and multivariate model we did not observe any association with BMI for the occurrence of DR but protective effect was shown with BMI <18.5 compared to those with BMI 18.5-24.99 (normal) in 15 year follow-ups. However the risk of DR was notably higher for the over weight and obese individuals but significant association was not noted because of fewer subjects belonging in this groups (Table 3A & 4).

**Discussion:**
Epidemiological surveys have shown that various risk factors are associated with diabetic retinopathy. Our data suggest that glycaemic control, measured either by FBG or 2-hr ABF and HbA1C were the strongest risk factors for 5, 10 and 15 years of incidental cases of diabetic retinopathy controlling for potential confounding factors. In addition, among lipids TG, TC and higher blood pressure were found to be significantly independent risk factors for the development of DR. Obesity measure like BMI were not found to be associated with the incidental case of DR.

**Glycemic control**
There is strong evidence to suggest that the development and progression of DR is influenced by the level of hyperglycemia (18, 19, 20). Univariate and multivariate model showed that high levels of FBG, 2-hr ABF and HbA1c were found to be significantly associated with DR in 15 year follow-ups and the mean values of these variables were also significantly high in patients with DR compared to NDR. It was observed in a study that glycosylated hemoglobin levels, was a significant risk factor for the long-term progression of diabetic retinopathy (21). In contrast to our findings, European population with retinopathy had worse glycemic control than patients without retinopathy in ten years after diagnosis (22).

**Hyperlipidemia**
In univariate model we found significant association with DR and high levels of TG in 15 year follow-ups and TC in 10 years DR while LDL and HDL-C were not associated with it. It was also found that the mean value of TG, TC and LDL-C concentrations were higher in DR compared to NDR. In CURES Eye study was also found similar association like our study (23). Several investigators have reported on the association of lipids with
DR, but the results have not been consistent. In this study serum lipids were not associated with DR in multivariate model. This may have postulated that other potential risk factors were associated with DR rather than serum lipids.

**Hypertension**

Many researchers have proved that hypertension is a risk factor for diabetic retinopathy. We have found the mean values of the systolic and diastolic hypertension were significantly higher among the DR compared to NDR patients. Previous study in Nepal showed that the development of diabetic retinopathy was twice more likely in hypertensive than non-hypertensive cases (24). The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure (25), while in the WESDR; diastolic blood pressure was a significant predictor of progression of diabetic retinopathy to PDR over 14 year follow-up in patients’ type 1 diabetes (20). On the other hand Oman and Japanese population studies demonstrated that hypertension had a strong association with DR (26, 27). It was also noted in univariate model that the association between systolic and diastolic hypertension with DR were significantly higher in 15 year follow-ups. On the other hand the multivariate model showed that systolic hypertension were significantly associated in first 5 year (p<0.05) and when it was adjusted for age in 15 years the association was more statistically significant (p<0.00).

**Renal disease**

Cross-sectional (28) and longitudinal studies (29, 30) report a relationship between microalbuminuria, proteinuria and retinopathy. In this study it is important to point out that there was a significant trend with increasing level of serum creatinine in patients with DR compared to NDR. It was also noted in univariate and multivariate model that the higher level of serum creatinine was significantly associated with DR at 10 and 15 years when it was adjusted by age the risk was almost 5 times higher in the higher level of serum creatinine groups in 15 years.

**Age:** In univariate and multivariate model we found significant association with age and DR. When age was increased by 1 year the risk was 7.2% and 2.5% higher in 5 and 10 year (univariate model) and 6% higher (multivariate model) in first 5 years. Some studies
have shown that older age with DM is a risk factor for the presence of DR (31, 32). Another study in USA showed that elderly diabetic persons were 1.5 times more likely than age-matched non-diabetic persons to develop vision loss and blindness (33).

**Gender:** We did not find significant association with gender and DR. In both of univariate and multivariate analysis the risk of DR was slightly higher in females than male at the level of first 5 and 10 years compared to male.

**Area:** As in other study (34), our univariate and multivariate analysis indicated that the residence of urban (P<0.00 in univariate model) and semi-urban (P<0.05 in multivariate model) population were significantly associated with DR in 10 years.

**Education & Income Level:** We did not find any significant association between education and the income level with DR. But a protective effect was found in the level of under and above graduate compared to illiterate. A study in India (35, 36) found low educational attainment and low socioeconomic status was associated with blindness. On the other hand the risk of DR was higher in the middle income group at the level of 10 and 15 years compared to the poor and high income groups. This may have occurred due to higher participants in the middle income group compared to those two groups.

**Occupation:** Earlier studies have shown that persons currently employed or working had fewer or no diabetic complications, as compared to those not working (37). Similar trend was noted with regard to employment/work in our study that employed or working persons had significant protective effect compared to unemployed at first 5 years in univariate and multivariate model. This may have occurred unemployed people to ignore these complications.

**BMI:** Recent studies have shown that DR may not only be associated with glycaemic control and blood pressure, but also to body mass index (BMI) in patients with type 2 diabetes (38, 39). Zhang et al (40) in the diabetes control and complications trial (DCCT) observed that besides diabetes duration and metabolic control, BMI had a significant predictive value in developing retinopathy. In our study we did not find any association
with BMI for the risk of DR but inversely a protective effect was shown with BMI <18.5 compared to those with BMI 18.5-24.99 (normal) in 15 year follow-ups. However the risk of DR was notably higher for the over weight and obese individuals but significant association was not found because of fewer subjects belonging in this groups.

Physical Activity Level (PAL) and diet: We did not observe any association between PAL and diet in this study. But physical activity level was found to be lower in subjects with DR compared to NDR and the fiber intake was significantly lower (g/day, P=0.008) in DR compared to NDR groups. However, the mean vitamin A (mg/day) intake was found to be slightly lower in subjects with DR compared to NDR. Despite the fact, we did not postulate the association between PAL and DR in this follow-up study because we did not have the record for dietary history and PAL in 5 and 10 years.

The Limitations of the study are that it is hospital based and from baseline to 10 years we did not have any information on diet and the physical activity level of the patients. That is why we could not speculate about causality and the relationship between the diet and the physical activity level with DR. However, further research should also be done to determine whether there is any association with these mentioned factors with DR. Physical activity and diet counseling by a physician or skilled healthcare personnel or dietitian are needed to increase the modify life-style as well as improving glycemic control. The strengths of our study are that it is long-term follow-up, which allow ascertainment of risk factors of DR, conducted on a large sample or population of Bangladesh so the results should be interpreted with caution but would like to have the representation of the diabetic patients in Bangladesh since BIRDEM is a tertiary hospital covering diabetes care for whole of Bangladesh. Further this may call for closer cooperation between the diabetologists and ophthalmologists to reduce the risk of complications and thereby improved quality of care.

Acknowledgements
We acknowledge the contribution of our team members and the physicians for their continuous effort in the collection of data. We also thank all the participants in the study for their active participation.
Table 1: Clinical, Biochemical and Anthropometric characteristics of the patients with DR and NDR over 4 Years (at inclusion 1993 to 15 years 2008)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>1st year (n=977)</th>
<th>5 year (n=DR-115+ NDR-862)</th>
<th>10 year (n=DR-151+ NDR-711)</th>
<th>15 year (n=DR-229+ NDR-482)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index (BMI)</strong></td>
<td>DR</td>
<td>24.3±3.5</td>
<td>24.0±2.8</td>
<td>24.3±3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>24.0±3.0</td>
<td>23.9±3.0</td>
<td>24.0±3.0</td>
<td>24.1±2.9</td>
</tr>
<tr>
<td><strong>FBG (mmol/L)</strong></td>
<td>DR</td>
<td>11.0±3.7*</td>
<td>10.5±2.7*</td>
<td>10.91±3.1*</td>
<td>10.91±3.1*</td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>10.5±3.9</td>
<td>8.6±2.9</td>
<td>8.5±2.5</td>
<td>7.4±1.8</td>
</tr>
<tr>
<td><strong>2-hr ABF (mmol/L)</strong></td>
<td>DR</td>
<td>16.06±4.8*</td>
<td>15.4±3.8*</td>
<td>16.5±4.1*</td>
<td>16.5±4.1*</td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>16.8±5.4</td>
<td>13.2±4.2</td>
<td>12.9±3.8</td>
<td>11.7±2.7</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>DR</td>
<td>9.6±2.6* (n=29)</td>
<td>9.9±2.1* (n=119)</td>
<td>10.38±2.1*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>8.7±2.5 (n=15)</td>
<td>7.7±2.3 (n=222)</td>
<td>8.0±2.3 (n=526)</td>
<td>7.27±1.5</td>
</tr>
<tr>
<td><strong>TC (mg/dl)</strong></td>
<td>DR</td>
<td>204.5±47.1</td>
<td>210.0±42.9*</td>
<td>216.4±45.1*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>193.9±50.5</td>
<td>196.5±46.5</td>
<td>198.7±43.0</td>
<td>204±40.5</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dl)</strong></td>
<td>DR</td>
<td>129.6±45.6 (n=38)</td>
<td>131.5±43.8 (n=90)</td>
<td>137.8±43.4*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>122.2±43.1 (n=51)</td>
<td>127.2±44.7 (n=250)</td>
<td>124.3±42.5 (n=336)</td>
<td>130±38.5</td>
</tr>
<tr>
<td><strong>HDL-C (mg/dl)</strong></td>
<td>DR</td>
<td>37.7±7.5 (n=36)</td>
<td>38.8±6.7 (n=91)</td>
<td>38.9±7.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>39.8±7.1 (n=52)</td>
<td>38.5±7.01 (n=256)</td>
<td>39.0±7.0 (n=340)</td>
<td>39.1±6.8</td>
</tr>
<tr>
<td><strong>TG (mg/dl)</strong></td>
<td>DR</td>
<td>199.4±88.5* (n=273)</td>
<td>192.2±74.3</td>
<td>200.0±86.4*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>172.6±84.3</td>
<td>170.7±71.9</td>
<td>179.5±71.7</td>
<td>180.1±70.5</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td>DR</td>
<td>1.15±0.35*</td>
<td>1.36±0.44*</td>
<td>1.8±0.74*</td>
<td></td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>NDR</td>
<td>0.99±0.24</td>
<td>1.07±0.3</td>
<td>1.14±0.37</td>
<td>1.11±0.42</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>DR</td>
<td>130±12.3*</td>
<td>129±11.7*</td>
<td>132±11.2*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>124±12.1</td>
<td>126±11</td>
<td>125±10.8</td>
<td>123±9.1</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>DR</td>
<td>84±8.31*</td>
<td>83±7.0*</td>
<td>85±6.0*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NDR</td>
<td>80±8.3</td>
<td>80±7.5</td>
<td>81±7.6</td>
<td>79±5.6</td>
</tr>
</tbody>
</table>

The result is expressed as mean±SD and student t’ test was done for appropriate significant test.
*P<0.05 for NDR group vs DR group.

n=subjects, DR=Diabetic Retinopathy, NDR=No Diabetic retinopathy, FBG=Fasting Blood Glucose, ABF= After Break Fast, TC=Total Cholesterol, TG= Triglyceride, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, LDL-C=Low density lipoprotein-cholesterol, HDL-C=High density lipoprotein-cholesterol, HbA1c= Glycosylated hemoglobin.
Table 2: Nutrient intake of the patients with DR and NDR at the stage of 15 year

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Total Intake among NDR (n=482)</th>
<th>Total Intake among DR (n=229)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate (g/day)</td>
<td>317.01±84.25</td>
<td>309.52±64.85</td>
<td>0.193</td>
</tr>
<tr>
<td>Fat (g/day)</td>
<td>17.84±7.66</td>
<td>17.69±7.51</td>
<td>0.795</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>66.15±16.95</td>
<td>67.41±16.18</td>
<td>0.340</td>
</tr>
<tr>
<td>Fiber (g/day)</td>
<td>6.50±2.52</td>
<td>5.97±2.42</td>
<td>0.008</td>
</tr>
<tr>
<td>Vitamin C (mg/day)</td>
<td>81.80 (77)</td>
<td>86.84 (85)</td>
<td>0.334</td>
</tr>
<tr>
<td>Vitamin A (mg/day)</td>
<td>723.99 (891)</td>
<td>693.91 (820)</td>
<td>0.804</td>
</tr>
<tr>
<td>Total Calorie (kcal/day)</td>
<td>2032.82±413.46</td>
<td>1986.82±323.47</td>
<td>0.107</td>
</tr>
</tbody>
</table>

The result is expressed as mean±SD, median (interquartile range) and student t’ test was done for appropriate significant test. n=subjects, DR=Diabetic Retinopathy, NDR=No Diabetic retinopathy.
Table 3: Socio-demographic factors associated with the development of DR in type 2 diabetic patients during three different time periods

<table>
<thead>
<tr>
<th>Variables</th>
<th>5 years RR (95% CI)</th>
<th>10 years RR (95% CI)</th>
<th>15 years RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>1.072*** (1.05-1.09)</td>
<td>1.025*** (1.00-1.04)</td>
<td>1.003 (0.99-1.01)</td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Village</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Semi-urban</td>
<td>1.03 (0.5-2.1)</td>
<td>1.42 (0.8-2.4)</td>
<td>1.01 (0.6-1.5)</td>
</tr>
<tr>
<td>Urban</td>
<td>1.01 (0.9-1.5)</td>
<td>1.76*** (1.2-2.4)</td>
<td>1.23 (0.9-1.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>1.01 (0.7-1.4)</td>
<td>1.09 (0.8-1.4)</td>
<td>0.82 (0.6-1.0)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Under Graduate</td>
<td>1.33 (0.6-2.9)</td>
<td>0.72 (0.4-1.2)</td>
<td>0.84 (0.5-1.2)</td>
</tr>
<tr>
<td>Above Graduate</td>
<td>0.82 (0.3-1.9)</td>
<td>0.64 (0.3-1.1)</td>
<td>0.86 (0.5-1.3)</td>
</tr>
<tr>
<td>Income Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Medium</td>
<td>0.83 (0.5-1.2)</td>
<td>1.02 (0.7-1.4)</td>
<td>1.14 (0.8-1.5)</td>
</tr>
<tr>
<td>High</td>
<td>1.04 (0.6-1.6)</td>
<td>0.85 (0.5-1.3)</td>
<td>0.96 (0.6-1.3)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Employed</td>
<td>0.40*** (0.2-0.6)</td>
<td>0.76 (0.5-1.0)</td>
<td>1.13 (0.9-1.4)</td>
</tr>
</tbody>
</table>

*RR = Relative Risk, CI = Confidence Interval
*P=<0.05, **P=<0.01, ***P=<0.00
Table 3A: Biochemical, clinical and anthropometric factors associated with the development of DR in type 2 diabetic patients during three cohorts

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>5 years (RR in 95% CI)</th>
<th>10 years (RR in 95% CI)</th>
<th>15 years (RR in 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Blood Glucose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 mmol/L</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥7 mmol/L</td>
<td>3.57*** (1.9-6.5)</td>
<td>3.01*** (1.7-5.1)</td>
<td>4.94*** (3.1-7.7)</td>
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<tr>
<td><strong>2-hr ABF</strong></td>
<td></td>
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<tr>
<td>&lt;11.1 mmol/L</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥11.1 mmol/L</td>
<td>3.46*** (1.9-6.0)</td>
<td>3.05*** (1.9-4.8)</td>
<td>5.96*** (3.7-9.5)</td>
</tr>
<tr>
<td><strong>HbA1C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 (%)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥7 (%)</td>
<td>3.67** (1.3-10.2)</td>
<td>8.28*** (3.7-18.5)</td>
<td>7.39*** (4.3-12.6)</td>
</tr>
<tr>
<td><strong>TC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥200 mg/dl</td>
<td>1.26 (0.8-1.7)</td>
<td>1.36* (1.0-1.8)</td>
<td>1.22 (0.9-1.5)</td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;150 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥150 mg/dl</td>
<td>1.56** (1.0-2.2)</td>
<td>1.50** (1.0-2.1)</td>
<td>1.37** (1.0-1.7)</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;100 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥100 mg/dl</td>
<td>1.61 (0.7-3.5)</td>
<td>1.58 (1.0-2.5)</td>
<td>1.02 (0.7-1.3)</td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td></td>
<td></td>
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<tr>
<td>High mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Low mg/dl</td>
<td>1.30 (0.5-2.9)</td>
<td>1.07 (0.6-1.6)</td>
<td>0.84 (0.6-1.0)</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥1.5 mg/dl</td>
<td>1.53 (0.9-2.4)</td>
<td>3.15*** (2.3-4.1)</td>
<td>4.64*** (3.7-5.6)</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;140 mmHg</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥140 mmHg</td>
<td>2.19*** (1.3-3.5)</td>
<td>1.81** (1.1-2.8)</td>
<td>2.59** (2.1-3.1)</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
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<td></td>
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<tr>
<td>&lt;90 mmHg</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>≥90 mmHg</td>
<td>3.43*** (2.2-5.2)</td>
<td>1.52 (0.9-2.4)</td>
<td>2.03*** (1.4-2.7)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.99 normal</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;18.5 under weight</td>
<td>0.82 (0.2-3.1)</td>
<td>0.65 (0.1-2.4)</td>
<td>0.98 (0.4-2.0)</td>
</tr>
<tr>
<td>25-30 over weight</td>
<td>1.23 (0.8-1.7)</td>
<td>1.01 (0.7-1.4)</td>
<td>1.06 (0.8-1.3)</td>
</tr>
<tr>
<td>&gt;30 Obese</td>
<td>1.13 (0.4-2.6)</td>
<td>1.01 (0.4-2.1)</td>
<td>1.01 (0.5-1.7)</td>
</tr>
</tbody>
</table>

RR= Relative Risk, CI= Confidence Interval

*P=<0.05, **P=<0.01, ***P=<0.00  FBG=Fasting Blood Glucose, ABF= After Break Fast, TC=Total Cholesterol, TG=Triglyceride, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, LDL-C=Low density lipoprotein-cholesterol, HDL-C=High density lipoprotein-cholesterol, HbA1C=Glycosylated hemoglobin, BMI=Body mass index.
Table 4: Multivariate analysis in patients with DR by the following Risk factors during three different time periods

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>5 years RR (95% CI)</th>
<th>10 years RR (95% CI)</th>
<th>15 years RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.06*** (1.04-1.08)</td>
<td>1.01 (0.99-1.03)</td>
<td>1.01 (0.98-1.02)</td>
<td></td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>1.04 (0.7-1.5)</td>
<td>1.04 (0.7-1.4)</td>
<td>0.90 (0.7-1.1)</td>
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<tr>
<td><strong>Area</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Village</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Semi-urban</td>
<td>1.20 (0.6-2.3)</td>
<td>1.83* (1.0-3.1)</td>
<td>1.14 (0.7-1.7)</td>
</tr>
<tr>
<td>Urban</td>
<td>1.00 (0.8-1.2)</td>
<td>1.31 (0.9-1.8)</td>
<td>1.08 (0.8-1.4)</td>
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<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Unemployee</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Employee</td>
<td>0.59* (0.3-0.9)</td>
<td>0.83 (0.6-1.1)</td>
<td>1.07 (0.8-1.3)</td>
</tr>
<tr>
<td><strong>Fasting Blood Glucose</strong></td>
<td></td>
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</tr>
<tr>
<td>&lt;7 mmol/L</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥7 mmol/L</td>
<td>3.19*** (1.7-5.8)</td>
<td>2.55*** (1.5-4.3)</td>
<td>2.99*** (1.9-4.7)</td>
</tr>
<tr>
<td><strong>HbA1C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 (%)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥7 (%)</td>
<td>8.34*** (3.7-18.6)</td>
<td>3.45*** (1.6-7.3)</td>
<td>4.93*** (2.8-8.5)</td>
</tr>
<tr>
<td><strong>TC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥200 mg/dl</td>
<td>1.05 (0.7-1.4)</td>
<td>1.04 (0.7-1.3)</td>
<td>1.01 (0.8-1.2)</td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;150 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥150 mg/dl</td>
<td>1.35 (0.9-1.9)</td>
<td>1.35 (0.9-1.8)</td>
<td>1.26 (0.9-1.6)</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 mg/dl</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥1.5 mg/dl</td>
<td>1.37 (0.8-2.1)</td>
<td>2.66*** (2.0-3.5)</td>
<td>4.67*** (3.8-5.7)</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140 mmHg</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>≥140 mmHg</td>
<td>1.67* (1.0-2.6)</td>
<td>1.32 (0.8-1.9)</td>
<td>2.63*** (2.1-3.2)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.99 normal</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;18.5 under weight</td>
<td>0.66 (0.1-2.3)</td>
<td>0.64 (0.1-2.3)</td>
<td>0.95 (0.4-1.8)</td>
</tr>
<tr>
<td>25-30 over weight</td>
<td>1.28 (0.9-1.8)</td>
<td>1.01 (0.7-1.2)</td>
<td>1.00 (0.7-1.1)</td>
</tr>
<tr>
<td>&gt;30 Obese</td>
<td>1.40 (0.6-3.2)</td>
<td>1.21 (0.6-2.4)</td>
<td>1.13 (0.6-1.8)</td>
</tr>
</tbody>
</table>

RR= Relative Risk, CI= Confidence Interval
*P=<0.05, **P=<0.01, ***P=<0.00. **** SBP and **** Serum Creatinine was adjusted for age in 15 years and HbA1C was adjusted for age in 5 & 10 years. FBG=Fasting Blood Glucose, TC=Total Cholesterol, TG= Triglyceride, SBP=Systolic blood pressure, HbA1C= Glycosylated hemoglobin, BMI= Body mass index.
References


ANNEXES
Annex- 1

**Questionnaire**

INCIDENCE OF DIABETIC RETINOPATHY: A 15 YEAR FOLLOW UP IN A HOSPITAL POPULATION (BANGLADESH)

Identification Information

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<td>2</td>
<td>Reference Number</td>
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<tr>
<td>3</td>
<td>Name</td>
</tr>
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<td>4</td>
<td>Present Address</td>
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<td>5</td>
<td>Permanent Address</td>
</tr>
<tr>
<td>6</td>
<td>Contact Number</td>
</tr>
<tr>
<td>7</td>
<td>Age (years)</td>
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</tbody>
</table>

<p>| | |</p>
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<tbody>
<tr>
<td>8</td>
<td>Sex</td>
</tr>
<tr>
<td></td>
<td>Male 1</td>
</tr>
<tr>
<td></td>
<td>Female 2</td>
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</tbody>
</table>

| 9 | Area of living |
|   | Urban 1 |
|   | Semi-urban 2 |
|   | Rural 3 |

| 10 | Marital Status |
|    | Married 1 |
|    | Unmarried 2 |

| 11 | Monthly/Yearly Income |
|    | Poor 1 |
|    | Medium 2 |
|    | High 3 |

| 12 | Education |
|    | Illiterate 1 |
|    | Under Graduate 2 |
|    | Graduate and above 3 |

| 13 | Occupation |
|    | Employed 1 |
|    | Unemployed 2 |
**Investigation Report from Patient Registry/Diabetic Guide Book from 1993 to 2008**

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<th></th>
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<tbody>
<tr>
<td>1) Blood Sugar (mmol/L):</td>
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</tr>
<tr>
<td>Fasting</td>
<td></td>
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<tr>
<td>2-hr post glucose load</td>
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<td></td>
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<tr>
<td>HbA1C (%)</td>
<td></td>
<td></td>
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<tr>
<td>2) Lipid Profile (mg/dl):</td>
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<tr>
<td>TC</td>
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<td>TG</td>
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<tr>
<td>LDL</td>
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</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
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<tr>
<td>3) Serum Creatinine(mg/dl):</td>
<td></td>
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<tr>
<td>4) Anthropometric Measurement:</td>
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<td>Weight (kg)</td>
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<td>BMI:</td>
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<tr>
<td>Waste/Hip Ratio:</td>
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<td>5) Blood Pressure:</td>
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<td>Systolic (mmHg):</td>
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<tr>
<td>Diastolic (mmHg):</td>
<td></td>
<td></td>
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<tr>
<td>6) Diabetic Retinopathy</td>
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<tr>
<td>(Absent 1, Mild NPDR 2, Moderate NPDR 3, Severe NPDR 4, Very Severe NPDR 5, Early PDR 6, PDR with high risk criteria 7, PDR with ADED 8, Clinically not significant 9, Clinically significant 10)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Interviewer Signature
Date:
Annex- 2

Diabetic Guide Book- shown partly

Mosammat Hasaina

আমার নাম মসামত হাসিনা

ফেস হিস্ট্রি

তারিখ 15-09-93

রোগের লক্ষণ 2, 3, 4, 5, 6, 7 months

ডায়েটিক্স কন্ফিনেনের

পূর্বের চিকিত্সা

বয়স 38 years

পূর্ণ/মহিলা

উচ্চতা 165 cm ওজন 55 kg বাড়িত ওজন 55 - 65 kg

গামার নির্দেশনা 84/09 ১২/০ আর্বুজ ৪/০ আর্বুজ

স্নাতকীয় নৃস্মৃতি রেকর্ড

ভান্ডা ব্যাংক ক্লাব সাঙ্গীভূত

ফুটবল প্রতিযোগিতা

ফান্ডোস্কোপিক পরীক্ষা

উপরের প্রতি েলাক্ষি

Normal

Fundi - Normal

R after 1 year.

৫১
Annex- 3

Food List Album
Annex- 4

Consent form

Good morning/afternoon,
I am a Master degree student of International Community Health at the University of Oslo, Norway and a research fellow of BIRDEM. I am working on the project which is carried out with permission from the Norwegian Ethical committee (REK) and the Ethical Review Committee (ERC) of the Diabetic Association of Bangladesh (DAB). The purpose of the project is to investigate the 5 year, 10 year and 15 year incidence rate of retinopathy. Also to focus on the factors associated with the development of diabetic retinopathy and the result will serve as a baseline- data for the development of preventive measures necessary to control the epidemics in Bangladesh.

To do this, we have to collect information from diabetic patients and also conduct some examinations, which will help us to plan and realise the project. With your permission therefore, we will like to ask you some questions and also to conduct some examinations to know which factors are associate for developing diabetic retinopathy. We will begin by asking you the questions today and then, tomorrow morning you will come back and conduct the examinations. The reason is that some of these examinations give correct results only if conducted when you have not eaten. These examinations will include your weight, height, BP, and your blood sample. If these examinations are not in normal range which may develop diabetic retinopathy, we will inform you and will refer you to the eye department for further treatment and follow up. You are free to choose either to participate or not to participate. Choosing to participate will be advantageous to you for four reasons:

1. You will know whether your diabetes is under control or not
2. You will know whether you have any eye complications or not (diabetic retinopathy, which is the main complications of long term diabetes)
3. You will also know which factors are associated for developing diabetic retinopathy
4. Knowing your health status will help you take appropriate decisions regarding your health.
You can trust that any information you will give us, including the results of your examinations, will all be treated very confidentially. For that reason, it is important that the information you give be as correct and truthful as possible. You also have the right to withdraw from the project at anytime during the study without prior reasons. This will have no negative consequences on you.

Do you freely choose to participate in the project?

YES □ Continue
NO □ End

ID No-

I __________________________, accept to participate and provide information to the research work entitled ___________ with my full concern.

All the provided information would be used in the research and contribute in the development of health care system.

Signature or thump print: __________________________

Date-

Address-
Annex- 5

Pictures from the field work

Picture 1: Using Snellen’s Chart for Visual Acuity examination

Picture 2: Using Slit Lamp for eye examination
Picture 3: Fundus examination by indirect ophthalmoscopy

Picture 4: Taking dietary history from a patient
Picture 5: Measuring weight during study