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RESEARCH ARTICLE

STUDY OF RISK FACTORS OF RETINOPATHY IN POORLY CONTROLLED BANGLADESHI TYPE II DM SUBJECTS

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ABSTRACT

Diabetic retinopathy is retinopathy caused by complications of diabetes mellitus, which can eventually lead to blindness. It is an ocular manifestation of systemic disease which affects up to 80% of all patients who have had diabetes. The aim of the study was to determine the risk factors associated with retinopathy in Type 2 diabetes of Bangladeshi subjects. In this study with a standardized selection procedure a total number of 60 diabetic patients without retinopathy and 41 diabetic patients with retinopathy were purposively enrolled from the Chittagong Diabetic Hospital. Diabetic retinopathy was diagnosed by retinal color photography. Anthropometric and different biochemical parameters such as Glucose, Triglycerides, Total cholesterol, High Density Lipoprotein, Low Density Lipoprotein, and HbA1c which were measured by standard methods. Compared to those without retinopathy, diabetic patients with any retinopathy were significantly older and they were (52.73±10.33 versus 60.13±9.40 and the p value was <0.001), had longer duration of diabetes (5.04±4.4 and 8.85±3.52 and the p value was <0.001), higher systolic blood pressure (126.67±13.86 versus 135±14.5 and the p value was =0.005) and poor glycemic control (8.73±2.12 versus 12.4±2.22 and p value was <0.001). The mean serum cholesterol (P<0.001), serum triglycerides (P <0.001), Low-density lipoprotein (LDL) (P =0.020) concentrations were higher and High density lipoprotein (HDL) (p<0.001) was lower in subjects with diabetic retinopathy compared with those diabetic without retinopathy. Multiple logistic regression analysis revealed that after adjusting for age, gender, BMI (Body Mass Index), duration of diabetes, and smoking HDL cholesterol (OR = 0.898, 95% CI 0.815, 0.989, P = 0.028) and serum triglycerides (OR = 1.024, 95% CI 1.004, 1.044, P = 0.014) were associated with Diabetic Retinopathy (DR). Serum triglycerides and HDL are significantly associated with retinopathy in type 2 Diabetic subjects, independently of the traditional risk factors, longer duration and glycemic control.

INTRODUCTION

Diabetic retinopathy caused by complications of diabetes mellitus and is the fifth-leading cause of global blindness. It is an ocular manifestation of systemic disease which affects up to 80% of all patients who have had diabetes (1). Despite these intimidating statistics, research indicates that at least 90% of these new cases could be reduced if there was proper and vigilant treatment and monitoring of the eyes (2). Diabetic retinopathy affects 1.8 billion people, and represents 4.8% of the world's blindness. Patients with long-standing diabetes mellitus eventually develop DR (6). The longer a person has diabetes, the higher their chances of developing diabetic retinopathy (3). Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycemia-induced intramural pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls. These damages change the formation of the blood-retinal barrier and also make the retinal blood vessels become more permeable (4). Small blood vessels – such as those in the eye – are especially vulnerable to poor blood sugar (blood glucose) control. An overaccumulation of glucose and/or fructose damages the tiny blood vessels in the retina. During the initial stage, called nonproliferative diabetic retinopathy (NPDR), most people do not notice any change in their vision. Early changes that are reversible and do not threaten central vision are sometimes termed simplex retinopathy or background retinopathy (5). All people with diabetes mellitus are at risk – those with Type I diabetes (juvenile onset) and those with Type II diabetes (adult onset). The longer a person has diabetes, the higher the risk of developing some ocular problem. At present, the world prevalence of DR in patients with diabetes is about 30%. By 2025, 75% of people with diabetes will be living in developing countries, due to the westernization of their way of living (7). Currently, treatment recommendations for DR include focal laser photocoagulation in patients with clinically significant macular edema and panretinal photocoagulation for severe nonproliferative DR and proliferative DR, but before vision has been significantly affected (8). For refractory cases, intravitreal injections of steroids or of anti-VEGF drugs are a novel option (9).

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Treatment benefits decrease sharply if the treatment is applied too late (10). In a health care system where there is a scarcity of specialists, primary care personnel are the main providers of care. Training such non-ophthalmologist medical personnel to administer ophthalmological treatment to patients with diabetes may be effective (11). The nonproliferative form of diabetic retinopathy (DR) is characterized by a loss of pericytes from retinal capillaries, microaneurysm formation, increased retinal capillary permeability, thickening of the capillary basement membrane, and impaired perfusion. Progression of the disease to the proliferative phase, characterized by neovascularization of the retina, greatly increases the probability of vision loss and this can be compounded by macular oedema, a result of the breakdown of the blood–retinal barrier which occurs in both non-proliferative and proliferative DR (12). Large prospective studies of both type 1 and type 2 diabetics have shown that a tight control of glycemia reduces the occurrence of DR and other microvascular complications compared to diabetics on a conventional therapy (The Diabetes Control and Complications Trial Research Group 1993; United Kingdom Prospective Diabetes Study (UKPDS) Group 1998). Hyperglycemia therefore appears to be directly or indirectly implicated in the pathogenesis of diabetic complications. A consequence of elevated glucose levels in blood and tissues is increased modification of proteins, nucleic acids, and lipids with advanced glycation end products (AGEs) which can have profound effects on cellular function. Here, we will review the current views on the role of AGEs in the initiation and evolution of DR (13). The aim of this study was to determine the lipid profile, to measure the glycosylated hemoglobin, to measure SGPT and Blood pressure components, to compare the lipid profile in diabetic subject without retinopathy, diabetic subject with retinopathy and in the non-diabetic subject and finally to investigate the correlation between lipid profile, and other factors with Diabetic retinopathy of Bangladeshi subjects.

MATERIALS AND METHODS

Period of Study: This study was carried out during the period of July 2010 to February 2011.

Study design: It was a cross sectional study. The subjects were selected on the availability of patients.

Study Subjects: A total of 101 subjects were included in this study. Subjects were recruited purposively in the study. Individuals referred to Chittagong Diabetes Hospital, Chittagong. The above 101 study subjects were classified as 60 (Without Diabetic Retinopathy, DWR) diabetic subject and 41 diabetic subjects (With Retinopathy, DR). In case of diabetic subject with or without retinopathy, they were selected from ophthalmology department at Diabetic Hospital in Chittagong.

Inclusion criteria: Those who are agreed to include in this study by providing consent.

Exclusion criteria

i) Patient with serious co morbid disease (infection, stroke, myocardial infarction, major surgery, malabsorption etc,
ii) History of using drugs significantly affecting glucose metabolism (glucocorticoids, oral contraceptives containing levonorgestrel or high-dose estrogen, phenytoin, high-dose thiazide diuretics etc.)

Development of Questionnaire

A questionnaire was developed to obtain data recording demographic and socio-economic data such as age, sex, family history of diabetes, living status and educational status. The questionnaire also included anthropometric measurement, hyper tension, walking, smoking, betel leaf, blood pressure , serum creatinine, serum glutamate, pyruvate transaminase, total serum cholesterol, high density lipoprotein, low density lipoprotein serum triglyceride. The questionnaire were coded and pre-tested before finalization.

Anthropometric measurements

1. Height (m)

Standing height was measured using appropriate scales (Detect-Medic, Detect scales INC, USA) without shoes. Height was recorded to the nearest 5 millimeter.

2. Weight (kg)

The balance was placed on a hard flat surface and checked for zero adjustment before measurement. The subjects stood in the center of the platform wearing light cloths without shoes. Weight was recorded to the nearest 0.5 kg.

3. Calculation of BMI

Body mass indexes (BMI) of the subjects were calculated using standard formula. BMI= Weight (kg)/[Height (m)]^2

4. Measurement of Blood Pressure (BP)

Blood pressure was measured in sitting position, with calf at the level of the heart. After 10 minutes of rest a second reading was taken. Blood pressure was measured using barometric sphygmomanometer according to WHO-IHS criteria.

5. Collection of blood samples

Fasting blood was collected between 8.00-9.00 am. Venous blood (10 ml) was taken by venipuncture with the subject sitting comfortably in a chair in a quiet room. Then the patient was given 75 g of glucose in 250-300 ml of water and advised to drink in 5 minutes. Patient was advised not to smoke, not to take any food and to take rest in a chair for 2 hours. The next blood sample was taken 2h after glucose load. After 10-15 minutes blood sample was centrifuged for 10 minutes at 3000 rpm to obtain serum. Fasting and 2h serum glucose was measured in the same day. Subjects were finally selected from Fasting and 2h serum glucose values that fulfilled the inclusion criteria of this study. Fasting serum triglyceride, total cholesterol and HDL cholesterol were measured. Fasting serum insulin was measured later on.

Laboratory Methods

Estimation of Serum Blood Glucose (Randox laboratories UK)

Glucose was estimated by enzymatic colorimetric (GOD-PAP) method (Barham, Trinder, 1972).

Estimation of Total Cholesterol

Total cholesterol was measured by enzymatic endpoint method (cholesterol Oxidase/Peroxidase) method in auto

analyzer(Analyzer Medical system , Rome , Italy) using reagent of Randox Labortories, UK (Trider, 1988)

Estimation of Triglyceride

Triglyceride was measured by enzymatic colorimetric (GPO-PAP) method in the Hitachi 704 Automatic Analyzer (Analyzer Medical system , Rome , Italy) using reagents of RANDOX Laboratories Ltd., UK.(Trinder 1969).

Estimation of high density lipoprotein (HDL) cholesterol (Analyzer Medical system, Rome , Italy)

High density lipoprotein cholesterol (HDLc) was measured by enzymatic colometric (CHOD-PAP) method in auto analyzer using reagent of Randox laboratories, UK.

Estimation of LDL-cholesterol

The LDL-Cholesterol level in serum was calculated by using by Friedewald formula (Friedwald *et al.,* 1972).

Estimation of Fasting Serum Creatinine

Estimation of creatinine was done by alkaline-picrate methods using reagents from Randox Laboratories, UK.

Estimation of SGPT

SGPT was estimated by UV method using ALT (GPT)opt. kit (RANDOX) (IFCC,1980)

Estimation of Glycocylated Hemoglobin (HbA1C): Intended use

The assay used on the Dimension$^{(R)}$ clinical chemistry system is an in vitro diagnostic assay for the quantitative determination of percent hemoglobin A1C () in human anticogulated whole blood. Measurements of percent hemoglobin A1C are effective in monitoring long term glucose control in individuals with diabetes mellitus.

Hemoglobin Alc Measurement

The same aliquot of the lysed whole blood that is Transferred form the first cuvette to the second cuvette for the Hb measurement is also used for the measurement of HbAlc. The second cuvatte contains and anti-HbAlc antibody in a buffered reagent. Hemoglobin Alc in the sample reacts with anti-HbAlc antibody to form a soluble antigen-antibody complex. A polyhapen reagent containing multiple HbAlc epitopes is then added to this cuvette. The polyhapten reacts with excess (free) anti-HbAlc antibodies to form an measured turbidimetrically at 340 nm and Blanked at 700 nm and is inversely proportional to the concentration of HbAlc in the sample.

Statistical analyses

Data were expressed as mean±SD, median (range) and number where appropriate. Comparison between two groups was done using Students unpaired‘t’ test for normally distributed variables and Mann-Whitney U for skewed data. Multinomial logistic and multiple linear regression analysis were performed as appropriate. Statistical analyses using Statistical Package for Social Science (SPSS) for Windows version 12.

RESULTS

Clinical Characteristics of the Study Subjects

Age/Year: Mean age (±SD) in the Diabetic without Retinopathy (DWR) and Diabetic Retinopathy (DR) subjects were 52.73±10.33 and 60.13±9.40 years respectively which were significantly higher in DR group (Table 1).

Body mass index (BMI, kg/m^2): Mean (±SD) BMI in the DWR and DR subjects were 25.92±4.28 and 25.6±3.81 respectively which did not show statistically significant difference (Table 1).

Systolic blood pressure (SBP, mmHg): Mean (±SD) SBP in the DWR and DR were 126.67±13.86 and 135±14.5 respectively which was significantly (p=0.005) higher in DR group (Table 1).

Diastolic blood pressure (DBP, mmHg): Mean (±SD) DBP in the DWR and DR were 81.83±8.68 and 80.63±12.62 respectively which did not show statistically significant (Table 1).

Serum creatinine (mg/dl): Mean fasting serum creatinine (± SD) in DWR and DR were 0.92±0.24 and 1.02±0.27 respectively which was significantly higher in DR group (Table 1).

SGPT (U/L): Mean (±SD) SGPT value in DWR and DR subjects were 23.5±9.26 and 25.5±7.43 respectively which did not show statistically significant (Table 1).

HbA1c (%): Mean (±SD) HbA1c (%) value in DWR and DR subjects were 8.73±2.12 and 12.4±2.22 respectively which was significantly higher in DR group (Table 1).

Duration of Diabetes: Mean (±SD) Duration of Diabetes value in DWR and DR subjects were 5.04±4.4 and 8.85±3.52 respectively which was significantly higher in DR group (Table 1).

Fasting and postprandial serum glucose levels of the Study Subjects: Mean (±SD) fasting glucose in the DWR and DR subjects were 8.81±3.34 and 13.35±5.9 respectively. Mean (±SD) postprandial serum glucose in the DWR and DR subjects were 18.83±5.51 and 20.11±5.68 respectively (Table 2).

Lipids level of the study subjects

Triglyceride (TG, mg/dl): Mean (±SD) TG in the DWR and DR subjects were 165±75 and 185±65 respectively. Mean TG value in the DR group was significantly higher compared to the DWR (p<0.001). (Table 3).

Total cholesterol (mg/dl): Mean (±SD) total cholesterol in the DWR and DR subjects were 187±39 and 232±36 respectively. Mean total cholesterol was significantly higher in the DR group compared to the DWR (p<0.001) (Table 3).

High density lipoprotein cholesterol (HDL-c, mg/dl): Mean (±SD) HDL-c level in DWR and DR subjects were 43.61±9.97 and 34.60±9.77 respectively which was significantly higher in the DWR group compared to the DR (p<0.001) (Table 3).

Low density lipoprotein cholesterol (LDL-c, mg/dl): Mean (±SD) serum LDL-c value in DWR and DR subjects were 116.98±33.04 and 130.58±24.40 respectively which was significantly higher in the DR group compared to the DWR (p=0.020) (Table 3).

Table 1: Clinical and anthropometric measurements of the study subjects

Variables	DWR	DR	t / p Values
Age (yrs)	52.73±10.33	60.13±9.40	-3.631/<0.001
BMI (kg/m^2)	25.92±4.28	25.6±3.81	0.386/0.701
SBP (mmHg)	126.67±13.86	135±14.5	-2.892 /0.005
DBP (mmHg)	81.83±8.68	80.63±12.62	0.568/0.572
S Creat (mg/dL)	0.92±0.24	1.02±0.27	-1.791/0.076
SGPT (U/L)	23.5±9.26	25.5±7.43	-1.192/0.257
Duration of Diabetes	5.04±4.4	8.85±3.52	-4.450/<0.001
HbA1c (%)	8.73±2.12	12.4±2.22	-8.346/<0.001

Results were expressed as mean±SD. Unpaired Student's't' test was performed to compare mean difference between groups. DWR (diabetic without retinopathy); DR (diabetic retinopathy); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); SGPT (serum glutamate pyruvate transaminase); S. Creat (serum creatinine).

Table 2: Fasting and postprandial glucose levels of the study subjects

Variables	DWR (n=60)	DR (n=41)
F SG (mmoll^{-1})	8.81±3.34	13.35±5.9
PPSG (mmoll^{-1})	18.83±5.51	20.11±5.68

Results were expressed as mean±SD. DWR (diabetic without retinopathy); DR (diabetic retinopathy); FSG, (fasting serum glucose); PPSG (postprandial serum glucose).

Table 3: Lipids level of the study subjects

Variables	DWR	DR	t/p Values
TG (mg/dl)	165.80±75.	292.67±53.81	7.878/<0.001
T CHOL (mg/dl)	187.42±39.77	232.35±36.04	5.743/<0.001
HDL-c (mg/dl)	43.61±9.97	34.60±9.77	4.450/<0.001
LDL-c (mg/dl)	116.98±33.04	130±24	2.363/0.020

Results were expressed as mean±SD. Unpaired Student's't' test was performed to compare mean difference between groups. DWR (diabetic without retinopathy); DR (diabetic retinopathy); TG (triglyceride); T. Chol (total cholesterol); HDL-c (high density lipoprotein cholesterol); LDL-c (low density lipoprotein cholesterol).

Table 4: Percentage of duration variation in years among DWR and DR patients including presence and absence of Dyslipidemia.

		DWR (%)	DR (%)
Duration of Diabetes (year)	<5	70	21.95
	5 - 10	20	48.78
	>10	10	29.27
Dyslipidemia	Present	33.33	4.88
	Absent	66.67	95.12

Table 5: Association of risk factors with diabetic retinopathy

Variables	B	Std. Error	P	OR	95% Confidence Interval for Exp(B) Lower Bound	Upper Bound
Age	0.087	0.056	0.117	1.09	0.98	1.22
Sex	-0.246	1.017	0.809	0.78	0.11	5.74
SBP	0.104	0.062	0.092	1.11	0.98	1.25
DBP	-0.259	0.109	0.017	0.77	0.62	0.96
HbA1c	0.142	0.175	0.417	1.15	0.82	1.62
T Chol	0.046	0.031	0.140	1.05	0.99	1.11
HDL-c	-0.208	0.077	0.007	0.81	0.70	0.94
LDL-c	-0.027	0.032	0.404	0.97	0.91	1.04
TG	0.014	0.006	0.026	1.01	1.00	1.03

OR: (Odds Ratio), DR (Diabetic Retinopathy); TG (triglyceride); T Chol (total cholesterol); HDL-c (high density lipoprotein cholesterol); LDL-c, (low density lipoprotein cholesterol).

Logistic Regression Analyses: Table 4: shows the results of regression analysis using DR as the dependent variable. After adjusting for BMI and smoking, DBP (OR = 0.77, 95% CI 0.062, 0.96, P = 0.017), HDL cholesterol (OR = 0.81, 95% CI 0.70, 0.94, P = 0.007) and serum triglycerides (OR = 1.01, 95% CI 1.00, 1.03, P = 0.026) were associated with DR.

DISCUSSION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. It has become a major health problem all over the world. It is a chronic, debilitating disease, which is associated with a range of severe complications including renal disease, cardiovascular disease, and retinopathies. Early detection and meticulous management to prevent complications is the major challenge of diabetic care.

Diabetic retinopathy is one of the most common micro vascular complications of diabetes, affecting 80% of patients over 20 years duration of diabetes. Despite remarkable advances in the diagnosis and treatment of diabetic retinopathy and its associated complications, diabetic retinopathy remains the leading cause of blindness among

working –age individuals in the developed countries. Very few studies on these risk factors has yet been done among Bangladeshi type 2 diabetic retinopathy patients. For this reason the present study was undertaken to measure the prevalence of retinopathy in Bangladeshi Type 2 diabetic subjects and to measure the risk factors of poor control of glycated hemoglobin and retinopathy in patients with Type 2 diabetes mellitus in a Bangladeshi population. Numerous studies have shown an association of lipid fractions with macro vascular complications of diabetes (e.g. coronary artery disease), while relatively few have looked at the association of serum lipids with micro vascular complications such as DR and the available results are conflicting [14–26]. This could possibly be due to heterogeneity in subject selection with variable inclusion criteria, such as age range, gender, diabetes duration, ethnicity and differences in the methodology of assessment and classification of DR. Dornan *et al*. [14] first showed in a landmark study the association of LDL-cholesterol in subjects with DR. In the Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR), Klein *et al*. [15] reported an association of unadjusted serum cholesterol with severity of hard exudates in the macula. ETDRS study have also demonstrated the association of total cholesterol and LDL-cholesterol with the onset as well as severity of retinal hard exudates [17]. In another interesting study, van Leiden *et al*. [27] showed that the hard exudates in DR are related to elevated serum LDL-cholesterol concentrations. This is consistent with our findings of an association between total cholesterol, LDL-cholesterol and non-HDLcholesterol with DME in subjects with Type 2 diabetes. However, the association of total cholesterol was lost after adjusting for age and gender, whereas with HDL cholesterol it was attenuated when adjusted for HbA1c and BMI. LDL-cholesterol was significantly associated with DME even after adjusting for HbA1c and BMI. Our result is consistent with the study by van Leiden *et al*. [27], who showed an association between unadjusted triglyceride levels and DR in subjects with Type 2 diabetes. The report by the DCCT/EDIC group has also shown that the severity of retinopathy was associated with serum triglycerides after adjusting for gender in subjects with Type 1 diabetes [28]. However, Larsson *et al*. [26] reported no association between serum triglycerides and degree of retinopathy in subjects with Type 1 diabetes. Hove *et al*. [29] found no association between DR and triglycerides, total cholesterol and HDL-cholesterol in an unselected population of Type 2 diabetic patients from Denmark. Also, Sinav *et al*. [22] reported that while total serum cholesterol, LDL-cholesterol and HDL-cholesterol were related to PDR, serum triglycerides showed no association. In our study there was an overall association of DR with triglycerides and HDL but not with TG and LDL cholesterol. The mechanisms by which high serum lipids cause the development and progression of DR are not fully understood. It has been postulated that an increase in blood viscosity and alterations in the fibrinolytic system occur in hyperlipidaemia and lead to the formation of hard exudates [30]. Also, incorporation of triglycerides into the cell membrane may lead to changes in membrane fluidity and leakage of plasma constituents in the retina [31]. This results in haemorrhage and oedema in the retina. Also, high lipid levels are known to cause endothelial dysfunction [32, 33] through a local inflammatory response, with subsequent release of cytokines and growth factors, hypoxia, increase in LDL oxidation, etc. In animal models it has been shown that endothelial dysfunction in the diabetic vasculature results in blood–retinal barrier breakdown [33-35]. The strengths of our study are that it is population based, conducted on small population of chittagong as the demographics of Chittagong are similar to the rest of the Bangladeshi urban population, the results can be generalized to the whole of the urban population in Bangladesh.

The drawback of the study is that, because it is cross-sectional, one cannot speculate about causality and the relationship between lipid subfractions and retinopathy, as this would need a prospective follow-up study.

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