Lipid Profile and Electrolyte Imbalance are Associated with Diabetic Retinopathy in Bangladeshi Population

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ABSTRACT----

Background: Diabetic retinopathy (DR) is a micro-vascular complication which is the main cause of blindness among people with Diabetes Mellitus. Identification and mitigation of the risk factors associated with DR will help to reduce the visual disability in diabetic subjects.

Aims and objective: The study has been undertaken to explore the association of lipids profile and electrolytes with the diabetic retinopathy in Bangladeshi type 2 diabetic subjects.

Material and methods: In the present study, 63 people diabetic with retinopathy (DR) and 80 people diabetic without retinopathy (DWR) were studied along with 92 healthy controls without family history diabetes and prediabetes. Anthropometric parameters, glucose, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, glycosylated haemoglobin (HbA1c) and electrolytes Na^+, K^+, Cl^-, HCO_3^- were measured by standard methods.

Results: HbA1c of DWR group and DR group were 8.60±1.17 and 11.80±1.63 respectively. Total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) were significantly higher ($p<0.001$) in both DWR and DR group compared to the healthy control. Triglyceride was significantly ($p<0.001$) higher in the DR group but no difference was found in DWR compared to the control group. K^+ was significantly increased in the DR group. Na^+, Cl^-, HCO_3^- were significantly decreased in the DR group compared to control group.

Conclusion: These results indicate that diabetic retinopathy patients exhibit dyslipidemia and electrolyte imbalance. Hypertriglyceridemia along with electrolyte imbalance is one the major risk factors toward the progression of diabetic retinopathy.

Keywords—Lipid profile, HbA1c, Electrolytes, Diabetic retinopathy.

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1. INTRODUCTION

Diabetic retinopathy (DR) is a vascular disorder that affects the microvasculature of retina. Half of the diabetes mellitus affected populations have some degree of DR[1]. DR is a complication of diabetes mellitus that and is one of the leading causes of acquired blindness in adults. Patients with diabetes for more than 20 years duration are likely to be affected by DR with a chance of losing sight[2].

There are many factors related to the development and progression of diabetic retinopathy. Retinopathy in diabetic patients depends on carbohydrate metabolism as well as on other factors like poor diabetes control, dyslipidemia, insulin-dependent diabetes, hypertension, alcoholism, pregnancy, anemia, hypomagnesemia etc.[5-13]. However, it is possible to determine risk factors related to the development of retinopathy[4]. Duration of diabetes and degree of hyperglycemia have been found to play central role in DR, but maintaining only glucose level does not prevent the development of DR. Thus, other confounding factors related to the diabetes are postulated to have a causal role. Some pathological mechanisms for diabetes to retinopathy progression have been proposed. Although many of the risk factors of DR have been identified but role of these factors is still confusing.

Diabetic dyslipidemia characterized by elevated serum total cholesterol (TC), triglycerides (TG), low-density lipoproteins cholesterol (LDL-C) and high-density lipoproteins cholesterol (HDL-C) has been proposed as possible risk factors for DR[14, 15]. It was also reported that local productions of reactive carbonyl species by the peroxidation of lipids in lipoproteins in the vascular wall mediate recruitment of macrophages, cellular activation, and proliferation. Lipoxidation end-products cause chemical modification of vascular proteins which affect both the structure and function of the vascular wall[16]. Accordingly, it was proposed that hyperlipidemia might contribute to DR by endothelial dysfunction and breakdown of the blood-retinal barrier causes serum lipids and lipoproteins exudation[17].

Electrolytes perform a significant role in several body mechanisms, like acid-base balance, membrane potential, muscle contraction, nerve conduction, and control of body fluid[18]. Disturbance in electrolytes homeostasis may lead to physiologic disorders. Insulin has been shown to activate Na+/K+ -ATPase enzyme. Therefore, low serum insulin level reduces the enzyme with deregulation of Na+/K+ pump that results in impairment of Na+ and K+ transport in and out of the cells, glucose transport also impaired with the defect of Na+/K+ pump. Hyperglycemia in diabetes mellitus causes glucose-induced osmotic diuresis with resultant loss of body fluids and electrolytes[18]. Several studies reported that evaluated level of electrolytes is associated with hyperglycemia[19, 20]. A study by Javaid et al (2007), demonstrated that blood sugar lowering drugs causes electrolyte imbalance by lowering sodium and increasing potassium [20]. Another study by Yasmin et al (2006), found lower levels of all electrolytes i.e. sodium, potassium, chloride, calcium, magnesium, and phosphorus[21].

The risk factors for the development of DR have been established based on mainly from European and US studies. So far, no study had been done to explore the association of serum lipid and electrolytes with retinopathy in Bangladeshi type 2 Diabetic subjects as it is well established that racial variations are also a confounding factor of diabetic retinopathy. Based on the above context, the present study was designed to investigate association of lipid profile and electrolyte imbalance with diabetic retinopathy in type 2 diabetic Bangladeshi population.

2. MATERIALS AND METHODS

This cross-sectional observational study was conducted in Chittagong Diabetic Hospital, Chittagong, Bangladesh. A group of 63 diabetic with retinopathy (DR) people and 80 diabetic without retinopathy (DWR) people were included in this study. In the case of diabetic subjects with or without retinopathy, they were selected from the ophthalmology department at Diabetic Hospital in Chittagong. There was no specific predilection for race, religion, and socio-economic status. Ninety-two age sex and BMI matched healthy subjects without a family history of diabetes were recruited as controls from the friend circle as considering the same socio-economic status. Written consent was obtained from all the volunteers; clinical examinations were undertaken by a registered physician using a predesigned questionnaire. Patients with serious comorbid diseases (infection, stroke, myocardial infarction, major surgery, malabsorption, etc.) and history of using drugs significantly affecting glucose metabolism (glucocorticoids, oral contraceptives, containing levonorgestrel or high-dose estrogen, phenytoin, high-dose thiazide diuretics, etc.) were excluded from the study. Anthropometric measurements were taken using standard methods. Subjects were requested to come on a prescheduled morning after overnight fasting for the fasting blood sample; subjects were then given 75 gm of anhydrous glucose, dissolved in 250 mL water or breakfast for the diabetic subjects. Blood was taken venipuncture at fasting condition, and 2 h post glucose challenged. Serum glucose level was measured using the glucose oxidase method, lipid profile (total cholesterol, triglyceride, HDL cholesterol) was measured using an enzymatic-colorimetric method and LDL cholesterol was calculated using the formula: LDL cholesterol= total cholesterol-(HDL cholesterol + triglyceride/5). Glycosylated hemoglobin (HbA1c) was measured using turbidimetric inhibition immunoassay (Dimension clinical chemistry system).

Electrolytes such as, $Na^{+,}$ $K^{+,}$ Cl^{-} and HCO_3^{-} were measured by Selective Ion Electrodes (Biolyte 2000 automate analyzer).

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Program) software for Windows version 12 (SPSS Inc. Chicago. Illinois, USA). All data were expressed as mean SD (standard deviation), median, and/or percentage (%) as appropriate. The statistical significance of differentials between the values was assessed by ANOVA or Mann-Whitney U test (as appropriate).

3. RESULTS

Anthropometric and clinical status of the study subjects

Age, systolic blood pressure, diastolic blood pressure, serum creatinine, and SGPT were significantly higher in type 2 diabetic subjects without retinopathy (DWR) and type 2 diabetic retinopathy (DR) subjects compared to that in controls (Table 1). Waist to Hip ratio (WHR) was significantly higher in DWR and significantly lower in DR subjects compared to the control group. BMI was significantly higher in DR compared to control, but did not show any difference between DWR and controls. Fasting glucose and postprandial glucose (after 2h glucose challenged) were significantly higher in DWR and DR compared to Control. Glycosylated hemoglobin (HbA1c) was significantly higher in DWR and DR compared to control group.

Lipids level of the study subjects

Total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) were significantly higher in both DWR and DR groups compared to the controls. Triglyceride was significantly higher in the DR group, but no difference was found in DWR compared to the control group (Table 2).

Electrolytes status of the study subjects

The electrolytes of sodium ion (Na^{+}) were significantly lower in the DR group but no difference was found in DWR compared to the control group but potassium ion (K^{+}) was significantly higher in both DWR and DR groups compared to the control group (Table 3). In the case of chloride ion (Cl^{-}) was significantly higher in DWR compared to controls whereas DR subjects were significantly lower compared to controls. Bicarbonate (HCO_3^{-}) showed no difference between DWR and control group but DR was significantly lower compared to than in controls.

Correlation analyses

In diabetic retinopathy (DR) group HbA1c showed positive correlation with fasting serum glucose ($p<0.001$), 2h postprandial serum glucose ($p<0.001$), HCO_3^{-} ($p<0.016$). Whereas, in diabetic without retinopathy (DWR) group HbA1c showed a positive correlation with fasting serum glucose ($p<0.001$), 2h postprandial serum glucose ($p<0.001$)

4. DISCUSSION

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 80% of all patients who have had diabetes. In Bangladesh, approximately 6.1% of the population aged 20-79 years have diabetes and 1.54 million people with DR. Serum lipids claimed to play an important role in the development and progression of DR that has been evaluated worldwide with different studies[14,15]. This study was aimed to find the association of lipids and electrolytes with DR in Bangladeshi Type 2 DM subjects.

In the current study, higher LDL, Cholesterol ,TG and lower HDL were found in both DWR and DR group compared to control (Table 2). Elevated levels of VLDL-cholesterol, LDL- cholesterol, triglycerides and low levels of HDL-cholesterol is a common problem for patients with diabetes[22]. Several studies have reported the association of lipids with DR, but the results have not been consistent. Verges (2015) found a significant association between elevated serum total cholesterol and LDL-cholesterol with the severity of retinal hard exudation in patients with DR[23]. Chennai Urban Rural Epidemiology Study (CURES), showed that the mean serum TC, TG and non HDL-C levels were higher in patients with DR as compared to those without DR[24].

In our study, the mean TG level in diabetic with retinopathy was higher than in diabetes without retinopathy and it was statistically significant ($p < 0.001$). From the results, it can be predicted that higher levels of TG indicate risk for the development of retinopathy in diabetes. The result was consistent with previous reports found significantly higher TG levels compared to healthy control.TG was found higher only in the DR group compared to control that indicates it plays a major role in the development of retinopathy in diabetic subjects which is similar to the findings of other studies [14, 15]. Increased plasma levels of triglycerides in VLDL are known as common characteristics of dyslipidemia associated with type 2 diabetes[25]. The possible mechanism is the reduced action of insulin on adipocytes. It reduces the suppression of the hormone-sensitive lipase action on the stored TG, thus releasing large amounts of free fatty acids. Delivery of the released fatty acids to the liver increases the hepatic TG production and subsequently increased production and release of VLDL[26]. HbA1c indicates the glycemic control of diabetic subjects. The mean HbA1c level of DR group was 11.80±1.63. Hyperlipidemia was evident in the poor glycemic controlled DR and DWR group. The dyslipidemia was characterized by elevated total serum cholesterol, triglyceride, LDL-cholesterol. Hepatic production of VLDL is known to be suppressed by insulin, and thus lack of insulin action would promote its production[27].

The measurement of TG shows the possibility of being a successful approach to the monitoring of diabetic patients [28]. Individuals with elevated total serum cholesterol, low-density lipoprotein (LDL) cholesterol or triglyceride levels are more likely to have or develop retinal hard exudates, which can be associated with risk of vision loss, independent of the extent of macular oedema[29]. The progression to proliferative retinopathy was also shown to be related to serum triglycerides. Findings of a Study Group have been shown that cholesterol is related to all levels of retinopathy and triglycerides are associated with moderately severe non-proliferative and proliferative retinopathy[30].

In this study, serum Na+ level decreased sequentially in DWR and DR groups compared to the control group which was in line with Mirsamadi *et. al.* (2004)[31]. K^+ and Cl- were significantly higher in diabetic without retinopathy than the control group that is opposite to the finding reported by the study in the Nigerian population[33]. In diabetic retinopathy group, levels of Na+, Cl- and HCO_3^- were lower than the control group. Clayton *et. al.* studies reported significant differences between serum Na+ of those suffering from age-related cataract[32]. Significantly lower serum potassium in diabetics than in the control is in contrast with the role of blood glucose in potassium metabolism (high serum glucose enhances the movement of potassium from the extracellular fluid into the cells) that is evidenced by significantly lower serum K^+ in diabetics with poor glucose level. Both elevated and reduced serum K^+ have been found to have a profound effect on neurotransmission as well as cardiac functions[33]. Intracellular dehydration is associated with a shift of potassium out of cells into the extracellular space. Potassium shifts are further enhanced by the presence of acidosis and the breakdown of intracellular protein secondary to insulin deficiency. Moreover, insulin deficiency prevents re-entry of K^+ into the cells. Osmotic diuresis and ketonuria lead to an increase in K^+ loss in urine. This pattern of electrolyte disturbances is remarkably similar to that previously observed in people with diabetes mellitus[34]. In this study, severely elevated serum potassium with moderate sodium decrease was observed in the DR group which was consistent with the findings of Javaid et al (2007)[20]. In correlation analysis, HbA1c showed a significant positive correlation with BMI, Creatinine, and HCO_3^-.

Conclusion: Cholesterol, TG, and LDL-C level seems to be positively associated with DR. However, HDL was negatively associated with DR. Electrolyte K^+ ion was positively associated with Diabetic retinopathy but Na^+, Cl^-, HCO_3^- electrolytes showed inverse association with DR. The result indicates that dyslipidemia and electrolyte imbalance are risk factors in diabetic retinopathy patients.

Table 1. Anthropometries and Clinical characteristics of the study subjects

Variables	Control group n=92	Diabetic without retinopathy (DWR) n=80	Diabetic retinopathy (DR) n=63
Age (Year)	45.88±7.52	49.78±8.36	53.75±8.14
BMI (Kg / m^2)	23.59±1.82	24.15±3.36	25.21±3.28*
WHR	0.93±0.03	0.92±0.04*	0.94±.01*
S_BP (mm Hg)	118.80±7.71	128.18±10.28*	150.79±10.12*
D_BP (mm Hg)	77.66±5.15	86.75±8.96*	91.26±9.20*
S_GPT (U/L)	33.54±2.2	26.17±8.71*	29.91±7.86*
S_Crea (U/L)	0.71±0.14	1.04±0.32*	1.36±0.24*
HbA1c (%)	5.45±0.35	8.60±1.17*	11.80±1.63*
F_Glu (mmol/L)	5.07±0.51	8.00±1.27*	12.06±1.61*
2h_Glu(mmol/L)	6.9±0.72	13.56±2.76*	19.83±4.83*

Results were expressed as Mean ± SD. Differences among the groups were calculated using ANOVA (Bonferroni 't' test) in the significance at 5% significance level n=number of subjects, BMI= Body mass index, WHR= Waist Hip Ratio, S_BP= Systolic Blood Pressure, D_BP= Diastolic Blood Pressure, S_GPT= Serum GPT, SCrea= Serum Creatinine, F_Glu= Fasting Glucose and 2h_Glu= After 2 hours Glucose. $p \leq 0.05$= significant.

Table 2: Lipid profile status of the study subjects

Variables	*C=92*	*Dwr=80*	*Dr=63*
S_Cholesterol	177.51±12.11	195.40±41.64**	221.46±22.42**
HDL-C	42.72±4.40	35.54±5.04**	31.60±3.49**
LDL-C	92.05±11.35	127.98±42.39**	142.33±20.72**
Triglyceride	187.13±27	191.67±75.21	307.46±55.96**

Results were expressed as Mean ± SD. Differences among the groups were calculated using ANOVA (Bonferroni 't' test) in the significance at 5% significance level n=number of subjects, S_Cholesterol = Serum Cholesterol, HDL-c = High-Density Lipoprotein cholesterol, LDL-C=Low Density Lipoprotein. $p \leq 0.05$= significant.

Table 3: Electrolytes status of the study subjects

Variables	*C=92*	*Dwr=80*	*Dr=63*
Na^+ (mEq/L)	140.85±20.89	139.33±12.02	128.96±7.23*
K^+ (mEq/L)	3.96±0.34	4.18±0.50*	5.15±0.64*
Cl^- (mEq/L)	102.12±3.63	103.43±5.45*	95.96±6.62*
HCO_3^- (mEq/L)	24.92±2.27	24.76±2.60	22.63±2.56*

Results were expressed as Mean ± SD. Differences among the groups were calculated using ANOVA (Bonferroni 't' test) in the significance at 5% significance level n=number of subjects, Na^+ = Sodium-ion, K^+ = Potassium ion, Cl^- = Cloride ion, HCO_3^- = Bicarbonate ion. p-value was calculated using log-transformed value. p less or equal to 0.05= significant.

Table 4: Correlation analyses for serum Na with different variables

Variables	Controls		DWR		DR	
	r	p	r	p	R	p
Age	-0.034	0.735	-0.007	0.948	-0.114	0.256
BMI	0.111	0.271	-0.046	0.650	-0.010	0.922
WHR	0.089	0.375	-0.192	0.056	-0.069	0.496
SBP	0.172	0.085	-0.052	0.609	-0.217	**0.029**
DBP	-0.125	0.214	0.008	0.937	-0.082	0.418
F_glu	-0.047	0.824	-0.125	0.550	-0.056	0.791
2h_glu	-0.160	0.446	-0.006	0.978	0.118	0.578
S_chol	0.328	**0.001**	0.093	0.357	0.041	0.687
HDL	-0.024	0.812	0.173	0.085	0.046	0.650
LDL	0.175	0.081	0.039	0.702	0.019	0.851
TG	0.007	0.946	0.009	0.933	-0.016	0.847
HBA1c	-0.091	0.367	-0.007	0.942	-0.044	0.663
S_creat	0.082	0.416	-0.203	**0.043**	-0.043	0.673
SGPT	0.046	0.648	0.051	0.617	-0.039	0.698
K	0.174	0.082	-0.211	**0.035**	0.000	0.999
Cl	-0.119	0.237	0.614	**<0.001**	0.390	**<0.001**
HCO3	-0.109	0.280	0.182	0.071	0.035	0.730
Duration	0.00	0.00	-0.105	0.296	0.051	0.611

Results were expressed as correlation coefficient (spearmans rho) r values. BMI= Body mass index, WHR= Waist Hip Ratio, S_BP= Systolic Blood Pressure, D_BP= Diastolic Blood Pressure, S_GPT= Serum GPT, SCrea= Serum Creatinine, F_Glu= Fasting Glucose and 2h_Glu= After 2 hours Glucose, S_Cholesterol = Serum Cholesterol, HDL-c = High Density Lipoprotein cholesterol, LDL-C=Low Density Lipoprotein, HbA1c= Glycosylated hemoglobin

Table 5: Correlation analyses for serum K with different variables

Variables	Controls		DWR		DR	
	r	p	r	p	r	p
Age	0.045	0.656	-0.029	0.777	-0.020	0.839
BMI	0.079	0.430	0.248	**0.013**	0.109	0.276
WHR	0.031	0.761	0.204	**0.041**	0.017	0.866
SBP	0.190	0.057	0.248	**0.013**	0.077	0.443
DBP	0.097	0.335	0.168	0.096	0.233	**0.019**
F_glu	-0.027	0.275	0.084	0.690	0.010	0.962
2h_glu	-0.115	0.584	-0.160	0.445	-0.122	0.563
S_chol	0.157	0.117	-0.041	0.686	0.093	0.356
HDL	-0.086	0.394	-0.044	0.664	-0.117	0.242
LDL	0.116	0.250	-0.035	0.728	0.122	0.223
TG	-0.028	0.777	0.059	0.563	0.065	0.519
HBA1c	-0.071	0.481	0.080	0.428	0.152	0.130
S_creat	0.098	0.333	0.131	0.195	0.097	0.336
SGPT	-0.099	0.323	0.048	0.636	0.127	0.209
Na	0.174	0.082	-0.211	**0.035**	<0.001	0.999
Cl	0.010	0.923	-0.179	0.074	-0.028	0.785
HCO3	0.085	0.396	0.048	0.637	0.108	0.283
Duration	-	-	0.147	0.146	-0.026	0.796

Results were expressed as correlation coefficient (spearmans rho) r values. BMI= Body mass index, WHR= Waist Hip Ratio, S_BP= Systolic Blood Pressure, D_BP= Diastolic Blood Pressure, S_GPT= Serum GPT, SCrea= Serum Creatinine, F_Glu= Fasting Glucose and 2h_Glu= After 2 hours Glucose, S_Cholesterol = Serum Cholesterol, HDL-c = High Density Lipoprotein cholesterol, LDL-C=Low Density Lipoprotein, HbA1c= Glycosylated hemoglobin

Table 6: Correlation analyses for serum HbA1c with different variables

Variables	Controls		DWR		DR	
	r	p	r	p	R	p
Age	0.069	0.496	-0.086	0.393	-0.064	0.525
BMI	0.068	0.498	0.140	0.166	0.197	**0.048**
WHR	0.106	0.291	0.033	0.741	0.003	0.976
SBP	0.019	0.847	0.127	0.207	-0.023	0.818
DBP	-0.070	0.488	0.165	0.100	0.024	0.810
F_glu	0.981	<**0.001**	0.659	<**0.001**	0.672	<**0.001**
2h_glu	0.722	<**0.001**	0.525	**0.007**	0.617	**0.001**
S_chol	0.120	0.233	0.039	0.700	0.036	0.722
HDL	0.031	0.757	-0.091	0.369	0.064	0.524
LDL	0.012	0.908	0.074	0.466	0.098	0.322
TG	0.128	0.203	0.012	0.903	0.064	0.525
S_creat	-0.005	0.959	-0.155	0.124	0.220	0**.027**
SGPT	0.056	0.580	-0.004	0.969	-0.026	0.797
Na	-0.091	0.387	-0.007	0.942	-0.044	0.663
K	-0.071	0.481	0.080	0.428	0.152	0.130
Cl	0.123	0.221	0.055	0.587	0.035	0.725
HCO3	0.109	0.276	-0.144	0.153	0.240	**0.016**
Duration	-	-	-0.008	0.936	0.248	0.012

Results were expressed as correlation coefficient (spearmans rho) r values. BMI= Body mass index, WHR= Waist Hip Ratio, S_BP= Systolic Blood Pressure, D_BP= Diastolic Blood Pressure, S_GPT= Serum GPT, SCrea= Serum Creatinine, F_Glu= Fasting Glucose and 2h_Glu= After 2 hours Glucose, S_Cholesterol = Serum Cholesterol, HDL-c = High Density Lipoprotein cholesterol, LDL-C=Low Density Lipoprotein, HbA1c= Glycosylated hemoglobin

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