ORIGINAL ARTICLE

ASSOCIATION OF GLYCEMIC CONTROL WITH SERUM LIPID PROFILE AMONG THE PATIENTS OF TYPE 2 DIABETES MELLITUS IN CHITTAGONG MEDICAL COLLEGE HOSPITAL

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ABSTRACT

Type 2 diabetic patients with poor glycemic control are more prone to dyslipidemia which has been suggested as a modifiable risk factor for the atherosclerotic macrovascular complications. Glycated hemoglobin (HbA1c) is considered as good indicator of long-term glycemic control as well as predictor of lipid profile. Early detection and treatment of lipid abnormalities can reduce the risk for cardiovascular disease in patients with type 2 diabetes mellitus (T2DM). Such type of studies in our country are limited. So we planned to evaluate the association of HbA1c with lipid profile among patients with type 2 diabetes at Chittagong Medical College Hospital, Bangladesh. This cross-sectional analytical study was carried out in the department of Biochemistry, Chittagong Medical College, Bangladesh from July 2020 to June 2021. A total 120 patients with T2DM aged 40-75 years were selected from outpatient department of Endocrinology, Chittagong Medical College Hospital by non-probability purposive sampling. Fasting blood glucose (FBG), HbA1c, fasting total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) were evaluated and lipid profile were compared between good glycaemic control (HbA1c $<7\%$) and poor glycaemic control (HbA1c $\geq 7\%$) group. There were 56 males and 64 females among 120 T2DM patients in this study. The mean age $\pm$ SEM (60.48 ± 1.06) of male patients was significantly higher than that of female patients (53.83 ± 1.26). There was a highly significant positive correlation between HbA1c and FBG ($r=0.854$, $p<0.001$). HbA1c and FBG had significant positive correlation with TC, TG, LDL-C, and significant negative correlation with HDL-C; the strength of significance for all lipid parameters being greater with HbA1c than FBG. Increased TC, TG, LDL-C, and decreased HDL-C were significantly associated with poor glycemic cases. HbA1c was a predictor of TC, TG, HDL-C and LDL-C in T2DM patients on linear regression analysis. The present study revealed that HbA1c significantly correlated with TC, TG, LDL-C and HDL-C. It is also found that there is a significant difference in lipid profiles between good and poor glycemic control cases. Thus, using HbA1c to monitor glycemic control may also have the added benefit of helping to identify type 2 diabetes people who are more vulnerable to cardiovascular complications.

Key words: Glycemic control, HbA1c, Lipids profile, Type 2 diabetes mellitus, Cardiovascular complications

Introduction

T2DM is a growing public health problem, with a significant impact on mortality, morbidity and economic loss globally because of changes in environmental factors like unhealthy diet, physical inactivity, overweight, obesity[1,2]. Bangladesh has also higher rates of morbidity and mortality related to diabetes[1,3]. According to International Diabetes Federation (IDF), approximately 13.1 million people were diagnosed with diabetes in Bangladesh which is the 8th position in the world, putting an enormous pressure on health system. This number is projected to reach 22.3 million with T2DM by 2045. Nearly, seventy-six thousand peoples were estimated to die because of diabetes-related complications in 2021[1]. In a Bangladeshi study it was found that loss of 4 million life years and 9.2 million (20.4%) Productivity-Adjusted-Life-Years (PALYs) were caused by diabetes. The loss in PALYs was equal to a total US$ 97.4; that billion lost (US$ 16987 per person) in GDP over the working lifespan[4].

T2DM is more prevalent (>90%) than other types of diabetes[5,6]. T2DM remains clinically silent for a long term. At the time of diagnosis of T2DM, nearly 30% individuals have chronic diabetic complications like cardiovascular disease (CVD), nephropathy, neuropathy, retinopathy[5,7]. Diabetes patients are often at risk to develop cardiovascular disease (CVD) CVD is the most common cause of mortality and morbidity in diabetic peoples[8].

T2DM with poor glycemic control are more likely to experience altered lipid metabolism resulting in atherogenic lipid profile known as dyslipidemia (elevated levels of plasma TC, TG, or both, or reduced levels of HDL). It plays a critical role for the development of CVD and associated with cardiovascular mortality when compared to people without diabetes[9]. Dyslipidemia is one of the risk factors for vascular complications in diabetic patients because it increases free fatty acid flux secondary to insulin resistance and exacerbated by increased inflammatory adipokine levels[9]. According to the Framingham Heart Study, in diabetic patients, the prevalence rates for high TC were 13% in males and 24% in females, and these rates for high TG were 19% in males and 17% in females[10]. In sevaral Bangladeshi studies, the prevalence rates of TG, TC, LDL were significantly higher, and HDL was lower in T2DM compared to non-diabetic individuals[11,12].

HbA1c is an important indicator of long term glycemic control with the ability to reflect the average glycemic control over the previous three months[13]. A HbA1c goal for many non-pregnant adults with DM is <7% (good glycemic control) without significant hypoglycemia[13]. Previous studies have reported that, HbA1c is considered as the test of choice for predicting dyslipidemia and cardiovascular disease (CVD) in diabetic patients[14,15]. In epidemiological analyses, HbA1c ≥7% (poor glycemic control) are associated with a significantly enhanced risk of both macrovascular and microvascular complications[13]. It has been found that good glycemic control can significantly reduce the risk of cardiovascular events in diabetic patients[16]. Vaag in his study has suggested that good glycemic control in patients with type 2 diabetes is more important than treating dyslipidemia for the prevention of both microvascular and macrovascular complications[17].

As increased HbA1c and dyslipidemia are risk factors of CVD, so diabetic patients with elevated HbA1c and dyslipidemia can be considered as a very high-risk group for CVD. Like in all other South Asian countries, T2DM and related cardiovascular complications develop 5-10 years earlier in Bangladesh than in western countries, so fatality rates are high among young adults[18]. Very few studies were conducted in Bangladesh to assess the relationship between HbA1c and dyslipidemia in T2DM patients and such kind of data in our district are still relatively scarce. So, to update, we planned to evaluate the association of HbA1c with lipids profile in peoples with T2DM attending at Chittagong Medical College Hospital, a tertiary care hospital of Bangladesh. Such data can fill in the gap of knowledge of scarcity of data and form the basis for early detection and treatment of lipid abnormalities, community awareness for glycemic control and that can minimize the risk for atherogenic cardiovascular disorders in patients with type 2 diabetes mellitus.

Materials and Methods

This cross-sectional anlytical study was conducted in the department of Biochemistry, Chittagong Medical College (CMC) Chattogram, Bangladesh from July 2020 to June 2021 for a period of one year. Samples were collected from 120 diagnosed cases of T2DM patients aged 40-75 years attending outpatient department of Endocrinology, Chittagong Medical College Hospital, using non-probability purposive sampling. People with other types of diabetes, thalassemia, known hepatic and renal diseases and having history of malignancy or with active infection were excluded from the study. After fulfilling the mentioned criteria, above objective and procedure of the study were explained in details and written informed consent was taken from each subject before inclusion in the study. Then they were requested to report to the department of Biochemistry, Chittagong Medical College following an overnight (8-10 hours) fasting for anthropometry and blood collection. Anthropometry included height (rounded to the nearest 0.5 cm), weight (rounded to the nearest 0.1 kg), waist circumference (rounded to the nearest 0.5 cm) and mean systolic and diastolic pressure (mm Hg) were measured using standardized protocols and calibrated equipment. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Blood pressure was measured by auscultatory method using mercury sphygmomanometer in sitting position with calf at the level of the heart after 10 minutes of rest. Then using standard phlebotomy techniques, fasting venous blood was collected into properly labelled three vacuum tubes containing serum tube (4 mL blood), EDTA tube (3 mL blood for HbA1c) and glycolytic tube (4 mL blood). Serum and glycolytic tubes were kept in standing position till clot formation. Then serum was separated by centrifuging at 3000 rpm for 5 minutes and blood samples were analysed using standard protocols. HbA1c was estimated in whole blood by ion-exchange high-performance liquid chromatography (HPLC) using Bio-Rad D-10 Haemoglobin Testing System. Glycemic status was categorized as good glycemic control if HbA1c was $<7\%$ and poor glycemic control if HbA1c $\geq 7\%$13. TC, TG, LDL-C and HDL-C were measured by enzymatic method using the ADVIA 1800 chemical auto-analyser. FBG was estimated by hexokinase method. Ethical clearance for this research protocol was taken from the Ethical Review Board of Chittagong Medical College (Memo No: CMC/PG/2020/662 date: 02/11/2020). Data were processed and analysed using IBM-SPSS (Statistical Package for Social Science) v25.0 for Windows. Data were

expressed as mean±standard error of means (SEM), frequency and percentages. P value <0.05 was considered statistically significant. Hypothesis testing was done by Chi-square ($\chi 2$) test, independent sample-t test, Pearson's correlation co-efficient, linear regression analysis.

Results

A total 120 T2DM patients (men 56; female 64) were selected in this study. The mean age±SEM (60.48±1.06 years) of male patients was significantly ($p<0.001$) higher than female patients (53.83±1.26 years). The female patients had significantly higher mean values for BMI (26.72±0.48, $p=0.03$) than male patients. The mean values of HbA1c and FBG did not differ significantly between males and females (Table I). The mean HDL-C (40.22±1.08 mg/dL, $p=0.004$) was significantly higher in female as compared to male (Table I). The mean values of TG were higher in female patients compared to male patients. Similarly, the mean of TC, and LDL-C were increased in male patients than female patients, but these differences were not statistically significant (Table I). HbA1c had increased (HbA1c ≥7%) in 84.2% of the cases. It indicates that most of the patients had poor glycemic control. It also found that most of the females (47.5%) had poor glycemia than male (36.7%) patients (Table II). Table III shows that increased TC, TG, LDL-C, and decreased HDL-C were significantly associated with poor glycemic cases. Both HbA1c and FBG exhibited positive correlations with TC, TG and LDL-C and negative correlation with HDL-C all these correlations were significant except FBG vs. HDL (Table IV). There was a highly significant positive correlation between HbA1c and FBG ($r=0.854$, $p<0.001$) (Fig. 1) The result from linear regression analysis observed that HbA1c was a predictor of TC, TG, HDL-C and LDL-C in T2DM patients (Table V)

Table I: Gender-wise comparison of clinical and biochemical characteristics of T2DM patients (n=120)

Variables	Male (n=56)	Female (n=64)	p value #
Age (years)	60.48±1.06	53.83±1.26	<0.001
Overall mean age (years)	56.93±0.88		
Weight (kg)	68.86±1.25	60.68±1.10	<0.001
Height (cm)	165.01±0.74	150.69±0.66	<0.001
Waist circumference (cm)	90.27±0.92	87.58±1.04	0.059
BMI	25.28±0.43	26.72±0.48	0.03
Systolic blood pressure (mm Hg)	139.77±2.5	134.91±1.64	0.09
Diastolic blood pressure (mm Hg)	84.43±1.22	85.11±1.00	0.66
HbA1c (%)	9.87±0.45	10.06±0.33	0.72
Serum FBG (mg/dL)	188.73±11.81	201.61±9.99	0.40
Serum TC (mg/dL)	210.18±5.6	201.92±5.9	0.31
Serum TG (mg/dL)	262.73±25.2	268.69±25.09	0.86
Serum HDL-C (mg/dL)	35.71±1.09	40.22±1.08	0.004
Serum LDL-C (mg/dL)	119.25±3.99	112.67±4.1	0.25

Results were expressed in mean±SEM. # Independent sample t-test.

Table II: Distribution of T2DM patients according to glycemic control (n=120)

T2DM patients	Male (n=56)	Female (n=64)	Total
Cases with good glycaemia, HbA1c<7%	12 (10)	7 (5.8)	19 (15.8)
Cases with poor glycaemia, HbA1c≥7%	44 (36.7)	57 (47.5)	101 (84.2)
Total	56 (46.7)	64 (53.3)	120 (100)

Results were expressed in frequency (percentages)

Table III: Association of HbA1c with serum lipids profile among T2DM patients (n=120)

Serum lipids profile		HbA1c < 7% (n=19)	HbA1c ≥ 7% (n=101)	p value
TC (mg/dL)	Normal	18 (94.7)	29 (28.7)	<0.001
	Increased ≥200 mg/dL	01 (5.3)	72 (71.3)	
TG (mg/dL)	Normal	14 (73.7)	15 (14.9)	<0.001
	Increased ≥150mg/dL	05 (26.3)	86 (85.1)	
HDL-C (mg/dL)	Normal	15 (78.9)	13 (12.9)	<0.001
	Decreased; M <40, F <50	04 (21.1)	88 (87.1)	
LDL-C (mg/dL)	Normal	17 (89.5)	18 (17.8)	<0.001
	Increased ≥100 mg/dL	02 (10.5)	83 (82.2)	

Results were expressed in frequency (percentages). Chi-square ($\chi 2$) test was done to find out p value.

Table IV: Correlation of serum lipids profile with HbA1c and FBG in T2DM patients (n=120)

Variables	HbA1c %		FBG mg/dL	
	Pearson Correlation (r)	p value	Pearson Correlation (r)	p value
Serum TC mg/dL	0.484**	<0.001	0.515**	<0.001
Serum TG mg/dL	0.350**	<0.001	0.428**	<0.001
Serum HDL-C mg/dL	-0.269**	<0.001	-0.160	0.081
Serum LDL-C mg/dL	0.482**	<0.001	0.458**	<0.001

**Correlation is significant at the 0.01 level (2-tailed)

Table V: Linear regression analysis of T2DM patients showing dependency of component of lipids profile on HbA1c (n=120)

Variables	Unstandardized coefficients *b*	p values
Serum TC mg/dL	7.2	<0.001
Serum TG mg/dL	22.4	<0.001
Serum HDL-C mg/dL	-0.77	0.003
Serum LDL-C mg/dL	4.47	<0.001

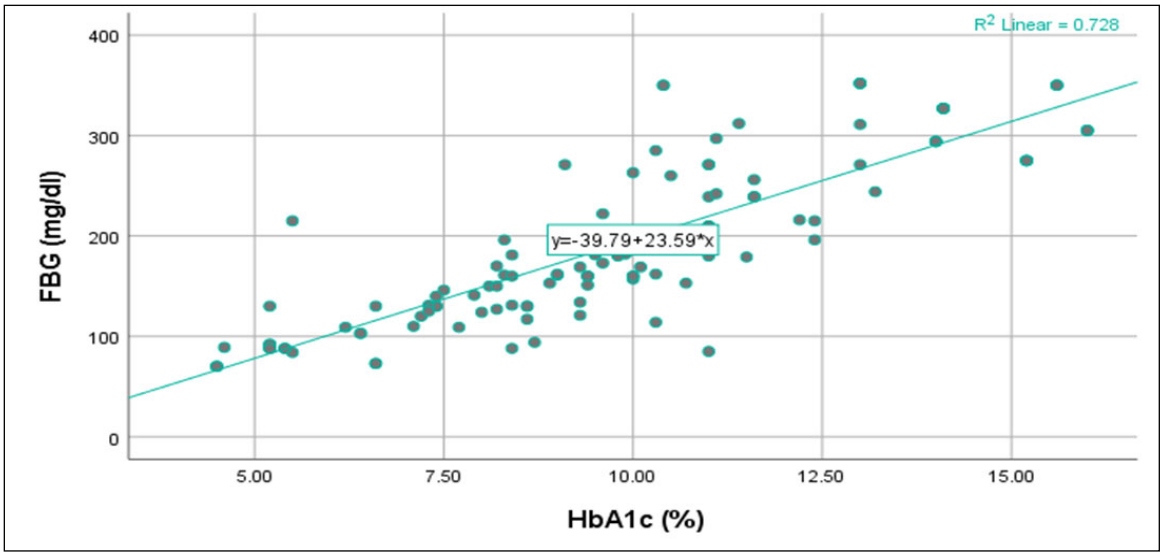

Fig 1. Scatter plot showing linear positive correlation between FBG (mg/dL)

Discussion

In this study out of 120 T2DM patients, there were more females (53.3%) than males (46.7%). It is in agreement with a previous study done by Majumder et al[19]. Overall mean age±SEM of the T2DM patients were 56.93±0.88 years and mean age (60.48±1.06 years) of male patients were significantly higher than that of female patients (53.83±1.26 years). Similar differences in age of type 2 diabetic patients have been reported by Singh and Kumar (mean age 50±11.8 years)[20]. The strong significant positive correlation between HbA1c and FBG (Fig 1) is in agreement with earlier reports[21].

Dyslipidemia is an important modifiable risk factor and associated with cardiovascular mortality in T2DM[9]. Diabetic dyslipidemia is caused by increased free fatty acid secondary to inflammatory markers and insulin resistance which directly downregulate Apo A-1 and HDL production while increasing the activity of key enzymes promoting hypertriglyceridemia. The characteristic features of diabetic dyslipidemia are elevated levels of plasma TG, small dense LDL, and reduced HDL[9],[22].

In the present study, the higher mean serum levels of TC, TG, LDL-C, and lower mean serum levels of HDL-C in both male and female were noted in T2DM patients. The possible reason of the increased dyslipidemia among the T2DM people are lifestyle changes such as consumption of western-style diets, reduced physical activity, and changes in type of work. These findings are in agreement with the findings of one previous study[23]. In this study, there were no significant differences between females and males in serum TC, TG, LDL-C compared but female patients had significantly higher mean values of HDL-C than males when compared. These findings were also observed in previous study[23]. However, Alzahrani et al found significant difference between males and females as TC, LDL, HDL compared[24]. It has been observed that diabetes plays a critical role for development of CHD in those patients whose HDL-C levels remain suboptimal despite successful lowering of LDL-C with statin[25].

The female patients had significantly higher values for BMI ($p=0.03$) These observations were consistent with previous study[24]. In spite of the availability of modern treatment tools for the management of diabetes, 84.2% of the T2DM patients showed poor glycemic control in this study. Same observations have been reported in Bangladesh in some previous studies[26,27]. In our study, increased TC, TG, LDL-C, and decreased HDL-C were significantly associated with poor glycemic cases. Similar observations of such association were found in different studies and suggested the critical role of poor glycemia in regulating dyslipidemia among patients with T2DM.[28] But many authors failed to find such association in T2DM[19]. HbA1c had significant positive correlation with TC, TG, LDL-C and significant negative correlation with HDL-C in T2DM patients. This result was consistent with the previous studies[15,23]. But this observation was inconsistent with the results of other studies[19,24]. Significant correlation were observed between HbA1c and serum levels of TC, TG and HDL-C ($p<0.05$) but no significant correlation of HbA1c value with LDL-C in diabetes patients[29].

The result from linear regression analysis showed that HbA1c was a predictor of TC, TG, HDL-C and LDL-C in T2DM patients. Hussain et al also reported same results[30]. However, Alzahrani et al[24] found HbA1c was associated with TG, while no significant associations were found with other components of lipid profile on regression analysis. The above discussion clearly indicates the clinical importance of glycemic control and lipid profile in the pathogenesis of cardiovascular disease among patients with T2DM. However, the literature indicates beneficial effects of increased physical activity, lifestyle changes and dietary modifications in improving glycemic control and dyslipidemia[31]. The significant association and correlation of HbA1c with all lipid parameters points towards the usefulness of HbA1c for screening high-risk diabetic patients. Type 2 diabetic patients with HbA1c $\geq 7\%$ tend to have severe dyslipidemia and therefore should be examined thoroughly for their lipid profile and associated complications.

One of the strengths of this study is that there was performing both HbA1c and fasting lipid profiles on T2DM subjects. To the best of our knowledge, it was the first study in CMC that looked at association between serum lipids profile and blood glucose among T2DM.

In the present study, it was found that lipid abnormalities in T2DM are hypertriglyceridemia, hypercholesterolemia, high LDL-C, and low HDL-C. HbA1c was significantly correlated with TC, TG, LDL-C and HDL-C. It also noted that a significant difference in lipid parameters between two groups of HbA1c. Therefore, HbA1c can be used as a marker for predicting dyslipidemia in patients with T2DM in addition to glycemic control. The optimal care for diabetic patients should include regular monitoring of HbA1c and lipid profile. The optimum treatment with proper antidiabetics should be continued with lipid lowering drugs as well as lifestyle modifications.

Multicenter prospective study with large sample size should be done in order to further evaluation of association of HbA1c with dyslipidemia among patients with T2DM. Inclusion of important variables like dietary habits, physical activity and treatment modalities may provide a better assessment of dyslipidemia in this context. Community based interventions should be aimed to convey awareness regarding maintenance of

target HbA1c (<7%) and regular monitoring of lipid profile along with lifestyle changes. These can help greatly to prevent or retard cardiovascular complications.

Limitations

This was a cross-sectional analytical study where causal relationships cannot be established. This was small sample study done by purposive sampling which cannot be generalized to the entire diabetic population. This study did not include important variables like dietary habits, lifestyle patterns and physical activity. We could not analyze data according to different treatment modalities.

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