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ASSOCIATION BETWEEN GLYCAEMIC CONTROL AND SERUM LIPID PROFILE IN TYPE 2 DIABETIC PATIENTS: GLYCATED HAEMOGLOBIN AS A DUAL BIOMARKER

Biochemistry

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ABSTRACT

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of cardiovascular diseases (CVD). This study is an attempt to evaluate the diagnostic value of Glycated haemoglobin (HbA_{1c}) in predicting diabetic dyslipidemia. Venous blood samples were collected from 294 type 2 diabetic patients. The whole blood and sera were analyzed for HbA_{1c}, fasting blood glucose (FBG) and lipid profile panel test. Dyslipidemia was defined as per the National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III guidelines. Diabetes was defined as per American diabetes association criteria. The statistical analysis was done by SPSS statistical package version 13.0.In our present study 92 (80.70%) females out of 114 and 150 (83.33 %) males out of 180 were found to be dyslipidemic. HbA1c demonstrated positive and significant correlations with total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and LDL-C ratio, non-HDL-C and TC/HDL-C ratio. Patients with HbA1c value > 7.0% had significantly higher value of TC, Triacylglycerol (TAG), LDL-C, LDL-C/HDL-C ratio, non-HDL-C and TC/HDL-C ratio as compared to the patients with HbA1c ≤ 7.0%. However, there was no significant difference in value of HDL-C between two groups. HbA1c can be used as a potential biomarker for predicting dyslipidemia in type 2 diabetic patients in addition to glycemic control.

KEYWORDS

Diabetes mellitus, Dyslipidemia, Glycated hemoglobin, Lipid Profile panel, Biomarker.

INTRODUCTION

Diabetes mellitus is a group of metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Diabetes causes about 5% of all deaths globally each year. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke).

Diabetic patients with accompanied (but often unnoticed) dyslipidemia are soft targets of cardiovascular deaths. Patients with type 2 diabetes often exhibit an atherogenic lipid profile, which greatly increases their risk of CVD compared with people without diabetes. An early intervention to normalize circulating lipids has been shown to reduce cardiovascular complications and mortality.

Glycated hemoglobin (HbA_{1c}) is a routinely used marker for long-term glycemic control. In accordance with its function as an indicator for the mean blood glucose level, HbA1c predicts the risk for the development of diabetic complications in diabetes patients. Apart from classical risk factors like dyslipidemia, elevated HbA1c has now been regarded as an independent risk factor for CVD in subjects with or without diabetes. Estimated risk of CVD has shown to be increased by 18% for each 1% increase in absolute HbA1c value in diabetic population. Positive relationship between HbA1c and CVD has been demonstrated in non-diabetic cases even within normal range of HbA1c. The aim of this study was to find out association between glycaemic control (HbA1c as a marker) and serum lipid profile in type 2 diabetic patients.

MATERIALS AND METHODS

Present study was conducted at Department of Biochemistry, JLNMC, Bhagalpur, Bihar associated with Department of Medicine, JLNMCH, Bhagalpur, Bihar. A total of 294 type 2 diabetic patients (180 males and 114 females) visiting the OPD of Medicine Department, Jawahalal Medical College and Hospital, Bhagalpur, Bihar from October 2017 to March 2019 were included in this study. Venous blood samples were collected from all the subjects after at least 8 hours fasting. The Serum was later used for analyzing Fasting Blood Glucosse (FBG), Lipid Profile Panel Test-Serum Total cholesterol(TC), HDL-cholesterol(HDL-C), Triacylglycerol (TAG), Risk ratio (TC/HDL-C) and Indirect LDL-cholesterol and Non-HDL Cholesterol (Non HDL-C) was calculated by Friedwald and Frederickson formula. HbA1c was estimated by using Ion exchange chromatography (Crest A Coral clinical system, USA).

For serum lipid reference level, National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guideline was referred. According to NCEP- ATPIII guideline, hypercholesterolemia is defined as TC>200 mg/dl, high LDL-C when value >100 mg/dl, hypertriglyceridemia as TAG >150 mg/dl and low HDL-C when value <40 mg/dl. Dyslipidemia was defined by presence of one or more than one abnormal serum lipid concentration. Diabetes was defined as per American Diabetes Association (ADA) criteria. The data were evaluated by SPSS statistical package version 13.0. Pearson's correlation test was performed to examine various correlations. Independent samples t-test (2-tailed) was used to compare means of different parameters. Value of HbA1c was given as percentage of total haemoglobin and values of all other parameters were given in mg/dl. All Values are expressed as mean ± standard error of mean. The results were considered non-significant when $P > 0.05$.

RESULTS

Among total 294 type 2 diabetic individuals included in this study, 180 were male and 114 were female. The mean age ± SEM of male and female subjects were 62.72±10.24 and 55.86 ± 12.08 years respectively. The mean value of HbA1c and FBG were slightly higher in females in comparison to male patients but the differences were not significant. Among the circulating lipids, TC and LDL-C were significantly higher ($P<0.05$) in females patients. Although the mean level of TAG was slightly lower and of HDL-C slightly higher in females than males, these differences were statistically non-significant (Table 1).

Table 1 : Lipid Profile parameters results of Male and Female Type 2 Diabetic Patients

Parameter	Male (n=180)	Female (n=114)	P-value
	Mean±SD	Mean±SD	
FBG	149.44±5.83	159.4±7.56	0.296
TC	177.03±3.99	196.68±7.23	0.011*
TAG	191.21±8.37	183.61±9.43	0.558
HDL-C	45.93±0.61	46.52±0.97	0.593
LDL-C	92.86±3.85	113.89±5.47	0.002*
HbA1c	7.20±0.10	7.53±0.17	0.105

*statistically significant

Hypercholesterolemia was found in 82(27.89%) individuals. Similarly, hypertriglyceridemia was found in 186(63.26%) individuals, decreased HDL-C was found in 46(15.6%) individuals and increased LDL-C was found in 140(47.6%) individuals. Among the diabetic individuals, 106(36.05%) individuals had only one abnormal lipid profile parameter, 88(29.93) had two abnormal lipid

parameter and 68(23.12%) individuals had more than 2 abnormal lipid profile parameter. According to NCEP- ATPIII guideline, 92(80.70%) females out of 114 and 150 (83.33 %) males out of 180 were dyslipidemic.

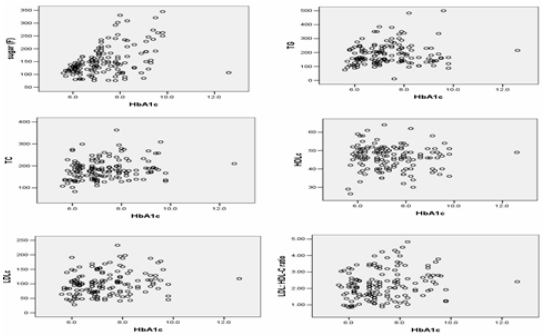
Highly significant correlation was observed between FBG and HbA1c (P=0.000). HbA1c also demonstrated direct and significant correlations with TC (P=0.017), LDL-C (P=0.015), LDL-C/HDL-C ratio (P=0.011), Non-HDL-C (P=0.011) and Risk ratio (P=0.005). The correlation of HbA1c with TAG was positive (P=0.169) and with that of HDL-C was negative (P=0.596) but it was statistically non-significant (Figure 1). Also, HbA1c was found to be a predictor of hypercholesterolemia (p=0.017; R^2=0.039) and high LDL-C (p=0.015, R^2 =0.040) by linear regression analysis. However, HDL-C (p=0.596, R^2 = 0.002) and TAG (p=0.169, R^2=0.013) did not show significant association with HbA1c in regression analysis.

Diabetic patients were classified into 2 groups as per their glycemic index; first group consists of patients with HbA1c value ≤7.0 % and second group consists of pa- tients with HbA1c value >7.0%. Patients with HbA1c value >7.0% had significantly higher value of TC (P=0.024), TG (P=0.030), LDL-C (P=0.011), Non-HDL-C, LDL-C/HDL-C ratio and Risk ratio as compared to the patients with HbA1c value ≤ 7.0% (Table 2).

Table 2 : Biochemical parameters categorized by patients glycemic control (HbA1c)

Parameter	Glycated Hemoglobin (HbA1c)		P-value
	≤7.0 (n=82)	>7.0(n=85)	
	Mean±SEM	Mean±SEM	
TC	174.89±5.29	181.78±5.19	0.024*
TAG	173.05±7.88	199.36±9.07	0.03*
HDL-C	46.79±0.84	45.71±0.68	0.322*
LDL-C	91.63±4.27	107.86±4.60	0.011*
Non HDL-C	127.03±4.72	149.20±5.32	0.002*
Risk ratio (TC/HDL-C)	3.76±0.098	4.31±0.127	0.001*
LDL-C/HDL-C	1.98±0.089	2.43±0.107	0.002*
FBG	123.56±3.03	175.0±6.79	0.000*

*statistically significant



DISCUSSION

In the present study, we have evaluated the pattern of lipid profile parameters in diabetic subjects and its correlation with HbA1c. The levels of HbA1c and FBG did not differ significantly between male and female. Although there were no significant difference in TAG and HDL-C levels between male and female, the levels of TC and LDL-C were significantly higher in female as compared to male type 2 diabetic patients. This finding is in agreement with the previous studies. Hyperlipidemia in females may be attributed to the effects of sex hormones on body fat distribution, which leads to differences in altered lipoproteins.

This study reveals high prevalence of hypercholesterolemia, hypertriglyceridemia, high LDL-C and low HDL-C levels which are well known risk factors for cardiovascular diseases. Insulin affects the liver apolipoprotein production. It regulates the enzymatic activity of lipoprotein lipase (LpL) and Cholesterol ester transport protein. All these factors are likely cause of dyslipidemia in Diabetes mellitus. Moreover, insulin deficiency reduces the activity of hepatic lipase and several steps in the production of biologically active LpL may be altered in DM. The main disorder in lipid metabolism was hypertriglyceridemia in our study. This finding is in concord with our previous study. In the study of Sehran et al in Pakistan, 54% diabetic individuals had elevated LDL-C and > 50% individuals had increased TG. These findings are similar to our study. But in contrast to our present study, they reported low HDL-C in 73% individuals.

A highly significant correlation between HbA1c and FBG in our study is similar with various previous studies. We also observed significant correlations between HbA1c and TC, LDL-C and LDL-C/HDL-C ratio. In various studies, HbA1c level was eminent as showing positive correlation with TC, LDL-C and TAG in diabetic patients. Our study also showed a significant correlation between HbA1c and non-HDL-C (P=0.009). Non-HDL-C was shown to be the stronger predictor of CVD in diabetic population by 'The Strong Heart Study' (data evaluated by Lu et al), with hazard ratios of 2.23 and 1.80 respectively in male and female. This study showed that increasing Non-HDL cholesterol concentrations had significant, curvilinear relationships with CVD and CHD risk (P <0.001). Moreover, NCEP ATPIII has recommended using Non-HDL cholesterol in assessing CVD risk in patients with diabetes. The correlation of HbA1c with non-HDL-C was found to be more significant than correlation of HbA1c with other lipid parameters except for LDL-C/ HDL-C and Risk ratio in our study. The measurement of Non-HDL-C is simple which can be conducted even in non-fasting state of patients and can be determined regardless of TAG concentration. Hence, Non-HDL cholesterol can be of great value in determining dyslipidemia in diabetic subjects. Risk ratio showed the strongest correlation with HbA1c in our study. In the prospective cohort study with inclusion of 418 Type 2 diabetic individuals with follow-up until the appearance of a cardiovascular event, Gimeno-Orna JA et al, showed that the main lipid predictor of vascular events was mean TC/HDL-C ratio with hazard ratio (HR) of 1.46. In the same study, the predictive power of the TC/HDL ratio was found to be higher than that of Non- HDL cholesterol and study concluded that TC/HDL-C can be used as a treatment guides for diabetic dyslipidemia. Total number of apo-B containing particles and small LDL-C Particles are increased in diabetes and these metabolic abnormalities are better reflected by TC/HDL- C ratio and Non-HDL-C than LDL-C alone. Significant association of HbA1c with various lipid parameters, Non-HDL-C, LDL-C/ HDL-C ratio and TC/HDL-C ratio in present study suggests the importance of glycemic control in order to control dyslipidemia.

The Diabetes complications and control trial (DCCT) established HbA1c as the gold standard of glycemic control. The level of HbA1c value ≤7.0% was said to be appropriate for reducing the risk of cardiovascular complications. In the present study, we divided diabetic patients into 2 groups as per the HbA1c cutoff of 7.0%. The diabetic patients with HbA1c value > 7.0% exhibited a significant increase in TC, LDL-C, TAG, LDL-C/HDL-C ratio, Non-HDL-C and Risk ratio without any significant alteration in HDL-C in comparison to patients with HbA1c value ≤7.0%. Khan HA et al showed the impact of glycaemic control on various lipid parameters in which the diabetic patients were categorized into 3 groups according to their HbA1c levels: group 1, good glycaemic control (HbA1c<6%); group 2, poor glycaemic control (HbA1c >6%–9%) and group 3, worst glycaemic control (HbA1c>9%). Though there was no significant differences in LDL–C in 3 groups with regard to glycaemic control, alterations in other lipid parameters were statistically significant in three different groups. Severity of dyslipidemia increases in patients with higher HbA1c value. As elevated HbA1c and dyslipidemia are independent risk factors of CVD, diabetic patients with elevated HbA1c and dyslipidemia can be considered as a very high risk group for CVD. Improving glycaemic control can substantially reduce the risk of cardiovascular events in diabetics. It has been estimated that reducing the HbA1c level by 0.2% could lower the mortality by 10%.

CONCLUSION

Significant correlation between HbA1c and various circulating lipid parameters and significant difference of lipid parameters in two groups (≤7.0% and >7.0%) of glycated hemoglobin indicates that HbA1c can be used as a potential biomarker for predicting dyslipidemia in type 2 diabetic patients in addition to glycemic control hence early diagnosis can be accomplished through relatively inexpensive blood testing.

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