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The role of glycated hemoglobin (HbA1c) and serum lipid profile measurements to detect cardiovascular diseases in type 2 diabetic patients

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Abstract

Patients with diabetes are considered to be at more risk of dyslipidemia and hypertension, hence targets for cardiovascular diseases. This study describes the possible role of Glycated Hemoglobin (HbA1c) and serum lipid profile as a biomarker in the detection of cardiovascular diseases. A cross-sectional study was carried out on 54 (33 males and 21 females) type 2 diabetes (T2DM) patients at Ayub Teaching Hospital (ATH), Abbottabad and Mardan Medical Complex (MMC), Mardan, Khyber Pukhtunkhwa (KP), Pakistan. The control group comprised of 20 (13 males and 7 females) healthy human samples. The patients had significantly higher (p<0.05) Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), HbA1c, Fasting Blood Glucose (FBG), Total Cholesterol (TC), Triglyceride (TG) compared to control subjects. Only High Density Lipoprotein (HDL) was found to be significantly (p<0.05) lower in the patients compared to controls. With regards to gender, in the female patients SBP, DBP, TC and Low Density Lipoprotein (LDL) were significantly higher (p<0.05) compared to males patients. The HbA1c was found to be significantly higher (p<0.05) in males. Results also revealed that patients having HbA1c>7.0%, had higher TG than those with HbA1c≤7.0%. Furthermore, 14.2% patients with HbA1c>7.0% had cerebrovascular diseases and 28% have ischemic heart diseases. The findings of the current study suggests association of HbA1c with lipid profile in T2DM patients and both might be used as a predictor of cardiovascular diseases in such patients.

Keywords: Diabetes mellitus, HbA1c, Lipid profile, Cardiovascular disease, Pakistan.

Introduction

Hyperglycemia is a metabolic syndrome that occurs due to defective secretion of insulin or insulin action.[1] The development of type 2 diabetes (T2DM) is a complex process and accounts for 85 to 90 % of all the diabetes mellitus (DM) cases. It has remained a major concern of healthcare professionals from long time due its strong association with cardiovascular diseases (CVD).[2]

Hypertension, a major risk factor for macrovascular and microvascular complications is found doubled in frequency in DM patients compared to normal population. It affects 40-60% of DM patients.[3-4] Similarly obesity is considered a risk factor for insulin resistance, cardiovascular and related diseases.[5-6] Patients with T2DM commonly experience dyslipidaemia contributing to the burden of the cardiovascular mortality.[7]

HbA1c reflects the average plasma glucose control over a period of 2-3 months therefore effectively used as a marker for evaluating glucose level.[1] It is the non-enzymatic binding of hemoglobin with glucose.[9-11] The Diabetes Complications and Control Trials (DCCT) recommended HbA1c to be a standard test for glycemic control, with levels ≤7% consider suitable for lowering the possibility of vascular complications.[12] However, this association between chronic hyperglycemia and macrovascular complications is not confirmed and

Practice Points

- Patients with T2DM are considered to be at more risk of dyslipidemia and hypertension, hence targets for cardiovascular diseases and complications.
- HbA1c can be considered as a standard test for glycemic control and HbA1c ≤7% and lower is suitable for lowering the possibility of vascular complications.
- Most of the microvascular and macrovascular complication in T2DM patients arise with an increase in HbA1c, dyslipidaemia and hypertension.
- The female patients experience more dyslipidemia and are more hypertensive than males but males are found to have poor glycemic control than females.
- HbA1c can potentially be used as a potential biomarker for the prediction of dyslipidaemia and CVD.

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defined. Several observational studies demonstrated that a higher HbA1c level was associated with increased risks of cardiovascular diseases and deaths.[13-15] On the other hand, a meta-analysis study showed that 1% HbA1c reduction was associated with a lowered major cardiovascular risks by glycemic control, but was not associated with lowered stroke and death risks.[16] Growing evidence supports the finding that HbA1c level is an independent risk factor for cardiovascular events, regardless of the diagnosis of diabetes.[17-20]

Therefore the current study was designed to investigate the role of HbA1c and lipid profile in detection of CVD events in T2DM patients.

Materials and methods

A hospital-based cross-sectional study was conducted from April to July 2013. The study populations were selected from the Ayub Teaching Hospital (ATH), Abbotabad, and the Mardan Medical Complex (MMC), Mardan, Khyber Pukhtunkhwa (KP), Pakistan. A total of 54 T2DM patients (33 males and 21 females) with average age of 56.5±11years were selected. The inclusion criteria for patients were those having diagnosed T2DM and visiting hospitals for review. A control group comprised of 20 healthy subjects (13 males and 7 females) with average age of 38.5±8.1years with no history of DM, hypertension and CVD.

Ethical consideration

The study was approved by ethical committee of the Department of Zoology, Hazara University, Mansehra, KP. Further written permissions were obtained from the Medical Superintendent of the mentioned hospitals where samples were collected. Informed consents were obtained from the patients as well as control subjects according to Helsinki Declaration.

Laboratory Investigations

Blood pressure of each patient and control was measured using BP apparatus. Fasting venous blood samples were taken from the patients for HbA1c, lipid profile and blood glucose. The HbA1c was expressed in percentage, blood pressure in mmHg and lipid profile and glucose unit were represented by mg/dl. Glucose was estimated by enzymatic oxidation of glucose oxidase. HbA1c was determined by fluorescence immunoassay methods with CHROMA reader System (SYCOmed, Germany). The lipid profile was determined using fully automatic computerized BS-400 Chemistry Analyzer (Mindray Medical International Limited, Shenzhen, P.R. China). The low density lipoprotein (LDL) Cholesterol was calculated using the following formula described by the Friedewald:[21]

LDL Cholesterol=TG (Triglycerides) – HDL (High Density Lipoprotein) - TG/5

Statistical analysis

All the data were presented in mean±SEM. Statistical analysis was performed using SPSS 20 versions. The *p*-value was calculated from online unpaired t-test by comparing mean±SEM. The p-value was considered statistically significant at <0.05. Further the relations of different variables with HbA1c were calculated using regression analysis.

Results

The current study involved 54 patients with T2DM while another 20 were selected without a DM history as a control. By comparing mean±SEM of T2DM with control, it was found that T2DM patients had significantly higher (p<0.05) HbA1c, fasting blood glucose (FBG), systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to the HbA1c, FBG, SBP and DBP of normal controls with similar body mass index (BMI) scores. The lipid profile of patients also showed significantly higher (p<0.05) total cholesterol (TC), total glycerides (TG), and lower HDL compared to TC, TG and HDL of normal control (Table 1).

Gender-wise analysis of the data revealed that females had significantly higher (p<0.05) SBP, DBP, TC and LDL compared to male patients. Male patients presented higher (p<0.05) HbA1c and FBG compared to females. Lipid profiles showed slight (p>0.05) increase in TG in female patients, and a similar non-significant (p>0.05) increase in HDL in males, but for TC and LDL a significant (p<0.05) increase was noted in females compared to males (Table 2).

Table 1: Comparison of BP, BMI, HbA1c, FBG and Lipid profile of T2DM patients with normal control subjects

Variables	Patients (n=54) Mean ± SEM	Control (n=20) Mean ± SEM	*p* value
Age (in years)	56.5 ± 11	38.5 ± 8.1	
SBP (mmHg)	133 ± 4	121 ± 2	0.0470*
DBP (mmHg)	82 ± 2	76 ± 1	0.0490*
BMI (kg/m^2)	26 ± 1	26 ± 0.4	1.000
HbA1c (%)	11 ± 0.3	5 ± 0.1	0.001*
FBG (mg/dL)	234 ± 21	65 ± 2	0.001*
TC (mg/dL)	166 ± 7	138 ± 7	0.0306*
TG (mg/dL)	235 ± 18	148 ± 9	0.0076*
HDL (mg/dL)	29 ± 1	38 ± 3	0.0305*
LDL (mg/dL)	79 ± 5	78 ± 7	0.092

Key: SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; HbA1c: Glycated Hemoglubin; FBG: Fasting blood glucose; TC: Total Cholesterol; TG : Triglycerides; HDL: High density lipoprotein; LDL: Low density lipoprotein. *Indicate statistical significance.

Table 2: Comparison of BP, duration of DM, BMI, HbA1c, FBG and lipid profile of male and female T2DM patients

Variables	Males (n=34) Mean± SEM	Females (n=34) Mean±SEM	*p*-value
SBP (mmHg)	126 ± 4	144 ± 6	0.0134*
DBP (mmHg)	79 ± 2	86 ± 3	0.0487*
Duration of DM (years)	9 ± 2	13 ± 1	0.0554
BMI (Kg/m^2	14 ± 3	16 ± 1	0.3950
HbA1c %	11 ± 0.3	10 ± 0.4	0.0438*
FBG (mg/dL)	237 ± 27	229 ± 29	0.8548
TG (mg/dL)	238 ± 26	229 ± 9	0.0821
TC (mg/dL)	154 ± 11	185 ± 26	0.0438*
HDL (mg/dL)	35 ± 6	41 ± 1	0.2466
LDL (mg/dL)	68 ± 9	97 ± 6	0.0090*

Table 3: Comparison of BP, duration of DM, BMI, HbA1c, FBG and Lipid profile of T2DM patients with HbA1c ≤ 7 and HbA1c >7

Variables	HbA1c≤ 7(n=5) Mean ± SEM	HbA1c>7 (n=49) Mean ± SEM	*p*-value
SBP (mmHg)	130 ± 11	133 ± 27	0.8133
DBP (mmHg)	76 ± 7	82 ± 13	0.330
Duration of DM	16 ± 2	10 ± 8	0.107
BMI (Kg/m^2)	25 ± 1	26 ± 4	0.59
TG (mg/dL)	113 ± 18	247 ± 20	0.039*
Risk ratio TC/HDL	4 ± 8	4.4 ± 3	0.81
LDL/HDL	2 ± 7	2 ± 2	1.00
FBG (mg/dL)	160 ± 61	233 ± 19	0.245
TG/HDL	4 ± 6	6.5 ± 7.3	0.46
TC (mg/dL)	122 ± 25	170 ± 8	0.05
HDL (mg/dL)	31 ± 3	38 ± 3	0.42
LDL (mg/dL)	62 ± 22	79 ± 6	0.346

The patient's data were categorized on the basis of HbA1c ≤7.0% and >7.0%. It was found that patients having HbA1c >7.0% have higher (p<0.05) TG levels compared to TG of patients having HbA1c ≤7 (Table 3). In the patients groups with HbA1c ≤7.0%, angina was recorded in 40% and macrovascular complications in 60%. Ischemic heart diseases (IHD) and stroke were not found in these patients. In patients with HbA1c >7.0%, IHD was recorded in 28%, angina in 19%, stroke in 14.2% and microvascular complication were found in 27% of the patients (Table 4).

Linear regression was used to know the dependence of HbA1c on different factors in T2DM. The negative dependence of SBP, duration of DM and positive relation of HDL was found to be statistically significant (p<0.05) (Table 5). Similarly in normal control subjects HbA1c showed only positive statistically significant (p<0.05) relationship with body mass index (BMI) (Table 6).

Table 4: Comparison of cardiovascular risk factors and microvascular complications on the basis of HbA1c

Variables	HbA1c ≤ 7 (n=5)	HbA1c >7 (n=49)
Stroke	0 %	14.2 %
Angina	40 %	19 %
IHD	0 %	28 %
Microvascular complications	60 %	27 %

Discussion

The present study demonstrates that T2DM patients experience severe dyslipidaemia and poor glycemic control and have significantly higher (p<0.05) TC, TG, lower HDL, HbA1c and FBG compared with non-diabetic control patients. The findings were supported by other studies conducted in India[22] and Pakistan,[23] which also reported significantly higher (p<0.05) TC, TG, LDL, low HDL, FBG and HbA1c in T2DM compared to the normal population. Increased levels of

Table 5: Relation of T2DM patient HbA1c with other variables

Variable	Unstandardized Coefficients β	*p* value
Constant	13.499	.000
Gender	-.958	.173
SBP	-.037	.024*
DBP	.034	.255
Duration of DM	-.124	.009*
BMI	.044	.564
Angina	-.691	.363
FBG	.002	.302
TC	-.019	.134
TG	.005	.096
HDL	.042	.044*
LDL	.007	.615
Stroke	-.762	.402
IHD	.408	.540

R^2= 0.407

Table 6: Relation of normal control HbA1c with other variables

Variables	Unstandardized Coefficients β	P value
Constant	-3.249	.269
Gender	-.563	.234
SBP	-.030	.310
DBP	.051	.289
BMI	.246	.022*
FBG	.024	.315
TC	-.009	.556
TG	-.003	.478
HDL	.068	.298
LDL	.007	.608

R^2 =0.625

all these parameters are suggestive of cardiovascular complications in DM patients. Other studies also compared hypertensive T2DM patients with controls and reported that increased levels of FBG, HbA1c and lipid profile are found in hypertensive T2DM patients compared to normotensive T2DM patients.[24]

In the current study, we did not find any significant difference for LDL in T2DM patients compared to controls. This difference may potentially be attributed to the difference in LDL calculation methods.[25] SBP and DBP were significantly higher (p<0.05) in T2DM compared to controls. Our results are also supported by similar studies in India[26] and in USA,[27] which showed significantly higher (p<0.05) SBP and DBP in T2DM patients compared to normal controls. The hypertension is also suggestive of cardiovascular complications in DM patients.

Females were found to be more hypertensive and hyperlipidaemic and have significantly higher (p<0.05) SBP and DBP, TC and LDL compared to SBP, DBP, TC and LDL of male patients. Similarly, previous studies also reported significantly higher (p<0.05) TC, LDL and HDL in female patients compared to male patients.[28-31] The hyperlipidaemia in female T2DM patients may be due to the sex hormones which are involved in the distribution of adipose in the body.[23]

Moreover increased dyslipidemia has been suggested to increase HbA1c and vice versa as the correlation between these parameters are directly proportional and goes hand-in-hand.[32,33] Reduction in HbA1c in T2DM is associated with improved insulin sensitivity and better lipid parameters. There are several mechanisms to elicit the effects of increased physical activity to improve dyslipidemia as it increases glucose removal and decreases muscle and hepatic insulin resistance through a number of mechanisms that would not necessarily be associated with changes in body weight.[34] However, increased physical activity and lifestyle modification seems to be associated with decreased HbA1c and better glycemic and lipid control. Thus, targeting to lower the dyslipidemia and obesity is likely to reduce HbA1c not only in diabetic subjects but it will have an equal effect in non-diabetic subjects.

In the current study it was further noted that HbA1c shows statistically significant (p<0.05) negative relation with SBP, duration of DM and positive relationship with HDL in T2DM patients which is comparable to the study conducted in India,[24] where significantly positive correlation was also reported of HbA1c with TC (r=0.29), HDL(r=0.19) and TG (r= 0.26).

The major limitation of this study is the small size of the studied population and confined in a defined geographical area. For this reason, the findings should be generalized with caution.

Conclusion

Patients with T2DM are considered to be at more risk of dyslipidemia and hypertension, hence targets for CVD and complications. The key findings of this study demonstrated that most of the microvascular and macrovascular complications in T2DM patients arise with an increase in HbA1c, dyslipidaemia and hypertension. The female patients experience more dyslipidemia and are more hypertensive than males but males are found to have poor glycemic control than females. HbA1c can potentially be used as a potential biomarker for the predictor of dyslipidaemia and CVD.

Conflict of interest

The authors declare no conflict of interest.

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