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HBA1C: ROLE AS A DUAL BIOMARKER FOR LONG TERM GLYCEMIC CONTROL AND INDIRECT INDICATOR OF DYSLIPIDEMIA IN TYPE 2 DIABETES MELLITUS

Pathology

Umesh Kumar Paliwal MD Associate Professor, Pathology, Rama Medical College, Kanpur, Uttar Pradesh

Rajeev Ranjan* MD Assistant Professor, Pathology, Government Medical College, Kannauj, Uttar Pradesh *Corresponding Author

ABSTRACT

Background: Dyslipidemia, frequently occurring in type 2 diabetic patients, might play a critical role in accelerated macrovascular atherosclerotic changes lead to lethal coronary artery disease thus, timely intervention by lipid lowering agents may reduce complications. Aim is to establish the role of HbA1c as dual biomarker for long term glycemic control and associated dyslipidemia. Total of 481 samples were taken from type 2 diabetic patients and analyzed for fasting blood sugar (FBG), Hba1c and Lipid profile(cholesterol, triglycerides, HDL, LDL and VLDL). Patients were categorized based on glycemic control into three groups; HbA1c< 6% as good, HbA1c>6% - <9% as poor and HbA1c>9% as worst glycemic control.

Results: HbA1c was directly correlated with cholesterol, FBS, TG, LDL and VLDL, however inversely with HDL

Conclusion: Study established role of Hba1c as dual biomarker for long term glycemic control and dyslipidemia in type 2 diabetic patients

KEYWORDS

HbA1c, Dyslipidemia, Glycemic control, Diabetes

Introduction

The word diabetes derived from the Greek means siphon (to pass through) and Latin word mellitus meaning honeyed or sweet, thus diabetes mellitus (DM) is known as sweet urine disease associated with marked loss of water by polyuria. DM is a common endocrine disorder characterised by hyperglycaemia and predisposes to chronic complications of eyes, microvasculature, nerves and kidneys[1].

HbA1c (Glycated hemoglobin) is frequently used as a marker of long term glycemic status over a preceding 8-12 weeks of time. Elevated HbA1c has also been regarded as an independent risk factor for cardiovascular disease (CVD) in subjects with or without diabetes[2]. Thus, elevated HbA1c has been proposed as an independent risk factor for both diabetics and CVD patients[3]. However, Glycemic control with decreased level of HbA1c is likely to reduce the risk of related complications[4]. Increased glycation particularly accumulation of tissue and serum glycated proteins have an actual role in the pathogenesis of diabetes related complications like retinopathy, cataract, atherosclerosis, neuropathy, nephropathy, diabetic embryopathy (newborn of diabetic mother) and impaired healing[1].

DM is rapidly gaining the status of a impending epidemic in India with >62 million diagnosed patients [5,6]. In 2000, India (31.7 million) topped the world with maximum number of patients with DM followed by China (20.8 million) and United States (17.7 million) in second and third place respectively. WHO has declared India as "Diabetic Capital of the world"[7]. According to Wild et al.[8], globally prevalence of DM is predicted to double from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 DM may rise up to 79.4 million cases in India, while China (42.3 million) and the United States (30.3 million) will also show significant rise by the disease [8,9]. There is a high risk of cardiovascular disease (CVD) in people with type 2 diabetes, also mortality by CVD is on the top cause in this population[10].

Dyslipidemia, frequently associated to type 2 diabetic patients, might have a pivotel role in accelerated microvascular atherosclerotic changes and may contribute to earlier CVD [11]. Early therapeutic interventions, to stabilize blood glucose value along with reduction in levels of TG, LDL and to increase HDL, significantly reduce atherosclerotic changes and mortality in patients with type 2 diabetes [12].

The aim of the study was to estabilishing the correlation of HbA1c as a dual biomarker for long term glycemic control and dyslipidemia in Type 2 diabetic patients.

Materials and methods

This retrospective cross-sectional descriptive study was conducted in Rama Medical College and lalpathlabs Kanpur with duration from September 2017 to august 2018. The data were obtained by reviewing the laboratory database. A total of 481 cases of non-hypertensive and non-obese patients of type II DM were included in this study with no other complain.

Inclusion Criteria

All diagnosed cases of Type 2 diabetes mellitus.

Exclusion Criteria

- Type 1 diabetics
- Patients on lipid lowering agents
- Chronic renal failure, Nephrotic syndrome
- Cholestatic jaundice
- BMI more than 30
- Known case of hypertension

Standard tests were used to analyze various parameters- blood samples were collected in strict aseptic precautions after overnight fasting. Informed consent from patients and detailed history were taken. Laboratory investigations were done as under –

- Estimation of serum glucose by Glucose oxidation method (GOD-POD method).
- Estimation of glycated haemoglobin (HbA1c) by high performance liquid chromatography
- Estimation of serum total cholesterol (TC) by cholesterol oxidase / phenol aminoantipyrine method.
- Estimation of serum triglycerides (TG) by enzymatic colorimetric end point method (glycerol phosphate oxidase – phenol) aminoantipyrine method.
- Estimation of serum High density lipoprotein (HDL) by cholesterol oxidase / phenol aminoantipyrine method
- Estimation of serum Low density lipoprotein (LDL) by Friedewald formula.
- Estimation of Very low density lipoprotein(VLDL) using Friedewald's equation.

For serum lipid reference level, National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guideline was referred. According to NCEP-ATP III guideline, hypercholesterolemia is defined as TCH > 200 mg/dl, high LDL when value > 100 mg/dl, hypertriglyceridemia as TG > 150 mg/dl and low HDL when value < 40 mg/dl. Dyslipidemia was defined as presence of one or more than one deranged serum lipid value [13].

The impact of HbA1c on various parameters was calculated by categorizing all the patients into three categories: HbA1c < 6% (good glycemic control), HbA1c 6–9% (poor glycemic control) and HbA1c >9% (worse glycemic control). The selection of these cutoff values of

HbA1c was based on earlier studies [3,14,15].

Statistical analysis

The data were analyzed by Microsoft office excel. Pearson's correlation test was done to examine various correlations. Independent samples Student's t-test was used to compare the means of different parameters between males and females. Post-hoc Dunnett's multiple comparison tests were used to examine the significance levels for various biochemical parameters in different age groups. Univariate analysis by one-way analysis of variance (ANOVA) was performed to evaluate the effects of gender, age and glycemic control on serum lipid profile.

Results

A total of 481 patients with Type 2 DM were included (338 males and 143 females as shown in figure 1. The mean age was 51.67 years (51.41for male and 52.29 for female) with age range of 18-90 years.

Table 1 showed good glycemic control is seen more commonly in female. Male exhibited higher value of fasting blood glucose (FBG) and Hba1c as compared to female in poor and worse glycemic control group.

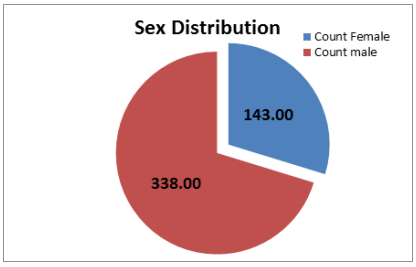

Figure 1 : Sex distribution among study population

Table 1 Distribution of subjects according to gender and HbA1C groups

Glycemic control	HbA1c criteria	Male		Female		Total Subjects	
		Number	Percentage	Number	Percentage	Number	Percentage
Good	≤ 6%	88	29.93	79	42.25	167	34.72
Poor	>6-9%	151	51.36	86	45.99	237	49.27
Worst	>9%	55	18.71	22	11.76	77	16.01
All Subjects	–	294	100	187	100	481	100

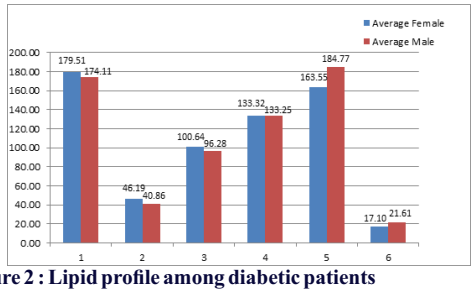

Figure 2 : Lipid profile among diabetic patients

Table 2 Serum biochemistry categorized by patient's gender

Parameters	Gender of Paitents	
	Male (N=294)	Female (N=187)
HbA1C	7.34±0.1178	6.98±0.1397
FBG	164.26±44.7542	151.12±31.2382*
Cholesterol Total	172.57±2.3929	180.66±3.086
HDL Cholesterol	40.54±0.4975	45.44±0.7152*
LDL Cholesterol	94.74±1.9742	102.04±2.4922
Non-HDL Cholesterol	132.03±2.2471	135.22±2.8805
Triglycerides	186.17±5.9768	166.34±6.073
VLDL Cholesterol	20.64±0.7652	19.68±0.936

All the values are in mg/dl except HbA1C which is reported as %
*P<0.001 versus males (t-test)

Gender wise comparison in values of HbA1c and lipid profile are shown in figure 2. Value of cholesterol, HDL (statistically significant) and LDL were higher in female patients, however TG levels are higher in males but difference is not significant (table 2). Patient's age was insignificantly correlated with glycemic control in both genders.
Serum biochemical parameters changes in different age group as shown in table 3. Older patients tend to have significant lower FBG, total cholesterol, LDL and VLDL (not statistically significant). Patient age and HbA1c showed no significant correlation in between, however younger diabetic patients (age<40years) showed relatively lower levels.

Table 3 Serum biochemistry categorized by patient's age

Parameters	Age of patients			
	≤ 50 Years(N=231)	51-60 Years(N=133)	61-70 Years(N=92)	>70 Years(N=25)
HbA1C	6.88±0.1342*	7.39±0.166*	7.7±0.180*	7.17±0.30*
FBG	142.07±8.416*	159.22±10.81*	176.12±9.573*	153.73±5.946*
Cholesterol Total	179.57±2.631*	177.61±2.85*	166.4±4.01*	161.3±5.94*
HDL Cholesterol	41.04±0.591*	43.09±0.82*	42.18±1.01*	43.84±1.56*
LDL Cholesterol	102.79±2.24*	98.72±1.152*	91.87±3.56*	82.33±6.24*
Non-HDL Cholesterol	137.52±2.701*	134.1±3.27*	124.22±4.16*	107.45±5.54#
Triglycerides	195.71±6.47*	159.95±5.69$	163.66±7.18	167.77±14.24
VLDL Cholesterol	21.7±0.916*	20.72±1.13*	18.63±1.11	14.41±2.00

All the values are in mg/dl except HbA1C, which is reported as %
* P < 0.001, # P < 0.01, $ P < 0.1

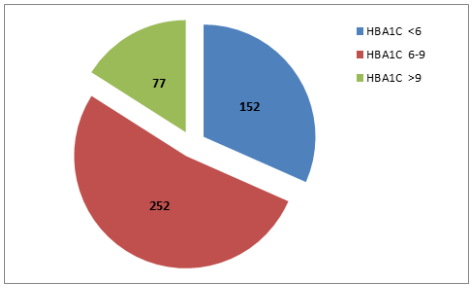

Figure 3 : Distribution of Patient with glycemic control

Table 4 Serum biochemistry categorized by different glycemic control (HbA1C) groups

Parameters	HbA1C		
	≤ 6% (N=167)	>6-9%(N=237)	>9%(N=77)
FBG	97.30±7.901*	176.43±13.498*	229.83±20.487*
Cholesterol Total	177.02±3.06	172.73±2.65*	183.65±4.86
HDL Cholesterol	43.43±0.741*	42.30±0.58*	40.27±1.02*
LDL Cholesterol	101.26±2.48*	94.37±2.21*	101.43±3.89#
Non-HDL Cholesterol	133.6±2.801	130.42±2.51*	143.38±4.36
Triglycerides	162.23±7.11#	179.94±5.78	209.69±8.63
VLDL Cholesterol	19.18±0.95*	20.05±0.79*	23.48±1.62*

All the value are in mg/dl
* P < 0.001, # P < 0.01

As table 4 showed division of glycemic control into three groups and comparing with the results of FBG and circulating lipids (Figure 3). There was a strong direct correlation between Hba1c and FBG having higher value in worse glycemic control. Patients with worse glycemic control (HbA1c>9%) had significant and direct increase in value of cholesterol, non-HDL cholesterol, TG and VLDL comparing to

patients of poor and good glycemic control, however significant inverse correlation is seen with HbA1c with HDL thus lowest level seen in worst glycemic control. Diabetic patients with poor (HbA1c 6–9%) and worse (HbA1c >9%) glycemic control had significantly higher levels of FBG (P<0.001) and triglycerides (P<0.01) and significantly lower levels of HDL (P<0.001) as compared to patients with good glycemic control (HbA1c ≤ 6%;Table 4). There was a significant increase in total cholesterol (P<0.001), LDL (P<0.001) and VLDL (P<0.001) in diabetic patients with worse glycemic control as compared to the poor glycemic control group.

Discussion

50-75% of deaths in diabetic patients are due to cardiovascular events [16]. Deranged HbA1c has been regarded as an independent risk factor for CVD in subjects with or without diabetes [17]. Our study showed strong direct significant correlation between HbA1c and FBG which is consistent with earlier studies [18,19,20]. Gender wise data shows that there is no significant difference in glycemic parameters and lipid profile between males and females except in HDL value which is significantly higher in females, consistent with earlier reports [21-25]. This may be resulted to the effects of sex hormones on body fat distribution, causing differences in altered lipoproteins [26]. Women with diabetes are more susceptible to increased mortality due to CVD [27].

Insulin modulates the production of liver apolipoprotein, which controls the enzymatic activity of lipoprotein lipase and Cholesterol ester transport protein. These could be the probable causes of dyslipidemia in DM as reported by Goldberg [28]. Most importantly, insulin deficiency reduces the activity of hepatic lipase and several other steps, in the production of biologically active lipoprotein lipase in DM [29].

A positive correlation between HbA1c and dyslipidemia was observed in the present study. Positive correlation of HbA1c level with TC and TG in diabetic patients has also been reported earlier [30]. Khan et al., also reported that severity of dyslipidaemia is directly proportional to higher HbA1c value [31]. Normalizing the glycemic levels may reduces the risk of CVD in diabetics. Khaw et al has found that reducing the HbA1c level by 0.2% could lower the mortality by 10% [32].

Levels of glycemic control in older patients were similar to younger ones. However, no significant difference between glycemic control levels and age wise distribution were found, which is supported by earlier study [33]. We observed significant decrease in cholesterol levels as age advances and TG levels significantly increases with worsening glycemic control consistent with earlier study [34]. Low HDL levels were seen with increased HbA1C value. High HDL levels protect against CVD development and vice versa [35,36].

Avogaro et al. [37] have reported that dyslipidemia in females type 2 DM and high FBG in males are significant risk factors and candidate for aggressive treatment.

The results of univariate analysis have shown that HbA1c is a good predictor of TG, then cholesterol, LDL and HDL. Eshaghian S et al., reported that HDL cholesterol is inversely, and non-HDL cholesterol directly, correlated with CVD risk in DM [38]. Onat et al. [39] suggested that fasting TG levels are predictive for impending CVD independent of all other parameters.

The above discussion clearly indicates that patients of type 2 DM with deranged circulating lipids are significant parameters of impending cardiovascular complications. Significant and linear relationship between HbA1c and dyslipidemia point towards the usefulness of HbA1c for screening diabetic patients at high risk of developing CVD.

Conclusion

This study confirms the HBA1C role as a dual biomarker for long term glycemic control as well as indirect indicator of dyslipidemia in male and female patients of type 2 diabetes mellitus as Hba1c provides valuable correlation of serum lipid profile. Hence Hba1c level may be used as screening test in diabetic patients for timely inteference of lipid lowering agents thus reducing risk of CVD.

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