

# Can HbA<sub>1c</sub> be a marker for cardiovascular risk in type 2 Diabetes Mellitus

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**Introduction:** One in every five Indians in geriatric age has diabetes. Diabetes is associated with increase in TG and apo B, with decrease in HDL component, so it contributes to atherosclerosis formation. We conducted a study to correlate glycaemic control using glycated haemoglobin with dyslipidaemia. **Methods:** The study is a cross sectional study with 200 diabetic patients, HbA<sub>1c</sub> was correlated with lipid profile and atherogenic index of plasma (AIP). AIP is log ratio of plasma triglyceride to HDL. Patients were categorised into good glycaemic control ( $\leq 7\%$ ) and poor glycaemic control ( $> 7\%$ ) based on glycaemic control with HbA<sub>1c</sub> as the marker. **Results:** Study showed the duration of diabetes directly correlates with HbA<sub>1c</sub>. None of the patients who had diabetes for more than 10 had HbA<sub>1c</sub> less than seven. BMI had direct association with HbA<sub>1c</sub>. HbA<sub>1c</sub> demonstrated a positive significant correlation with Total Cholesterol, LDL and a negative significant correlation with HDL. Atherogenic index of plasma directly correlates with HbA<sub>1c</sub> with mean AIP of  $0.36 \pm 0.24$  and  $0.58 \pm 18$  in good glycaemic control (GCC) and poor glycaemic control (PCC) respectively. Patients with HbA<sub>1c</sub>  $> 7.0\%$  had statistically significantly higher value of total cholesterol, LDL when compared with  $< 7.0\%$ . **Conclusion:** These findings clearly indicate that HbA<sub>1c</sub> can provide valuable supplementary information about the extent of dyslipidaemia, AIP. Screening for HbA<sub>1c</sub> estimation helps in preventing complications by achieving adequate glycaemic control. Thus, HbA<sub>1c</sub> can be used as a potential biomarker to identify patients with cardiovascular risk in Type 2 Diabetes Mellitus and can be used as a guide for aggressive therapeutic approach.

**Key words:** Diabetes, Atherogenic index, Dyslipidemia.

## Introduction

Type 2 diabetes is associated with insulin resistance in the target organ with hyperinsulinemia initially and loss of beta islet cell in later stages which leads to insulin deficiency. Incidence of diabetes now has exceeded what was expected 10 years ago and it's expected to increase further. Prevention of diabetes is of utmost importance for the primary care physicians. Patient can be asymptomatic for a long time before the diagnosis is made [1]. Diabetes is associated with many vascular complications. Alterations in lipid and lipoprotein profile contribute to atherosclerosis in type 2 diabetes. The atherogenic index of plasma (AIP), defined as logarithm [log] of the ratio of plasma concentration of triglycerides to high-density lipoprotein (HDL) cholesterol, has recently been proposed as a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk [2].

The aim of the study is to study the correlation of glycaemic control using glycated haemoglobin (HbA<sub>1c</sub>) with diabetic dyslipidaemia and atherogenic index of plasma. This investigation is an attempt to evaluate the diagnostic value of HbA<sub>1c</sub> in predicting cardiovascular risk by studying its correlation with atherogenic dyslipidemia, Atherogenic Index of Plasma with HbA<sub>1c</sub>

## Methods and Materials

Present study was conducted in S.P. Medical College & Associated Group of P.B.M. Hospitals, Bikaner. It was a cross sectional study and enrolled 200 Type 2 Diabetes patients attending medical outdoor, Geriatric care and research centre and those admitted in hospital. Before enrolment, details about nature and utility of present study were explained to all patients and informed consent was taken. All patients were subjected to detailed clinical examination and relevant investigations. Only after the

**Case Report**

inclusion and exclusion criteria were met, the subjects were included in the study.

Patients were classified into two groups depending on their glycated hemoglobin (HbA1c); Good Glycemic Control (GGC) group having HbA1c < 7.0% and Poor Glycemic Control (PGC) group having HbA1c >7.0%. For serum lipid reference level, National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guidelines were referred [3]. According to NCEP-ATP III guideline, hypercholesterolemia is defined as Total Cholesterol (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 in men and < 50 mg/dl in women. Dyslipidemia will be defined by presence of one or more than one abnormal serum lipid concentration. The atherogenic index of plasma (AIP), which is a predictive marker for plasma atherogenicity were measured as logarithm [log] of the ratio of plasma concentration of triglycerides to high-density lipoprotein (HDL) cholesterol with AIP < 0.11 low risk; AIP 0.11 – 0.21 intermediate risk and AIP > 0.21 increased risk. Venous blood samples were collected from all the subjects after at least 8 hours of fasting.

Diabetics with Family history of hyperlipidemia, with heart failure, respiratory, neurological, renal and malignant disorders, on lipid lowering therapy, thiazolidinediones and anti-inflammatory drugs, with abnormal liver function tests, with acute febrile illness, asymptomatic infections and chronic illnesses were excluded from the study. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 17). The P values <0.05 were considered statistically significant.

**Results**

Two hundred Type 2 Diabetes Mellitus patients comprising all age groups were recruited from the outpatient and inpatient department. There were 117 patients with glycated hemoglobin >7 and 83 patients with glycated hemoglobin <7. Following observations were made. Seventy patients had elevated total cholesterol levels with 54 patients (77.1%) with HbA1c>7, resulting in significant correlation between HbA1c and total cholesterol levels. Eighty one type 2 DM patients had elevated TG levels (>150mg/dl) with 69 patients (85.1%) with HbA1c>7, resulting in significant correlation

between HbA1c and serum triglyceride levels. About 132 type 2 DM patients had elevated LDL levels (>100mg/dl) with 79 patients (59.8%) with HbA1c>7, resulting in significant correlation between HbA1c and serum LDL levels. About 50 female type 2 DM patients had decreased HDL levels with 24 patients (48%) with HbA1c<7, resulting in no significant correlation between HbA1c and serum HDL levels in females. About 48 male type 2 DM patients had decreased HDL levels with 32 patients (66.6%) with HbA1c<7 resulting in no significant correlation between HbA1c and serum HDL levels. Patients were divided into three groups based on Atherogenic Index Plasma (AIP) into Low, Intermediate and Severe grades including 17, 18 and 165 patients respectively with 113 patients (68.4%) with HbA1c levels >7 with the difference being highly significant (p<0.001). FBS showed that the mean FBS level in HbA1c <7 group was 130.63 + 32.95 and the mean FBS in HbA1c >7 group is 174.78 + 66.18, with the FBS levels showing a significant correlation with the glycated hemoglobin. Distribution of the cases according to the age group showed 94 patients in 6-10 yrs group with 51 patients (54.2%) in HbA1c >7. The age groups 11-15 and >15 had all patients (100%) in HbA1c>7 group resulting in significant correlation of duration of diabetes with glycated hemoglobin. Out of total 83 patients with HbA1c <7gm%, 42 patients (50.60%) had normal BMI. In HbA1c >7 group, 3, 75, 16 and 23 patients were from underweight, normal, overweight and obese group and the difference was statistically significant (p<0.05). Out of total 69 females, 50 females had their WHR >0.85 with 32 females (64%) with HbA1c > 7. In males, 28 had their WHR >0.95 with 24 (85.71%) of them HbA1c<7. On statistical analysis, the difference was statistically highly significant (p<0.001). Distribution of cases according to residence showed that majority of patients belonged to rural areas with a total of 133 patients in which about 86 patients (64.66%) with HbA1c >7. In the HbA1c <7 group, 36 of the total 67 patients (53.73%) belonged to urban areas with significant correlation of glycemic control with patients of rural residence. Distribution of cases according to the socioeconomic status show that 157 patients (78.5%) belong to the lower and middle SES group out of which 82 patients (52.22%) belong to the poor glycemic control group with glycated hemoglobin showing significant positive correlation with socioeconomic status which may be due to the inability of the patients with lower incomes to afford adequate healthcare facilities which leads to poor glycemic control.

**Table 1:** Association of various parameters with Glycaemic control

Parameter	Good glycaemic control	Poor glycaemic control	P value
Duration of diabetes	5.54±2.87	8.91±5.22	<0.001
FBS	130.6±32.9	174.7±66.1	<0.001
BMI	22.8±2.09	27.01±5.06	<0.001
TC	173±32.5	190.6±34.9	<0.001
TG	116.6±95.9	166.2±54	<0.001
HDL-C	43.6±6	42.08±7.51	0.11
LDL-C	106.3±26.3	115.2±31	<0.05
AIP	0.36±0.24	0.58±0.18	<0.001

## Discussion

The prevalence of diabetes is increasing rapidly all over the world in last 20 years. India is often called the diabetic capital of the world as it about to overtake China in terms of prevalence. According to reports, in 2011 there were 366 million people with diabetes all over the world and it is expected to rise to 552 million by 2030 which is almost 80% increase [4]. The morbidity of diabetes is due to its complications which involves both macrovascular (stroke, peripheral vascular disease and coronary artery disease) as well as microvascular components (nephropathy, neuropathy and retinopathy) [5].

The percentage of glycosylated haemoglobin (HbA1c) reflects the glycaemic control of a patient during the 8-10 week period. The Diabetes complications and control trial (DCCT) established HbA1c as the gold standard of glycaemic control. Lowering HbA1C is one of the aims in diabetic treatment as it reduces microvascular and it also helps in controlling macrovascular complications if implemented early in the disease [6].

Major risk factor for the development of cardiovascular events in diabetes is dyslipidaemia. The classic features of diabetic dyslipidaemia are high plasma triglyceride concentration, low HDL cholesterol component and increased concentration of small dense LDL-cholesterol particles [7]. The LDL can be normal in diabetes. The LDL cholesterol found in diabetes is small dense molecule which is more atherogenic. Diabetics display enhanced LDL oxidizability and there is increased rate of atherosclerosis [8,9]. There is local release of hypochlorous acid from myeloperoxidase, which interacts with HDL molecule and decreases its action which is reverse cholesterol transport. There are various alterations in small dense LDL molecule which make it more atherogenic like reduced LDL receptor affinity[10], greater propensity for transport into the subendothelial space[11], increased binding to arterial wall proteoglycans. So it is prudent to prescribe statins to elderly diabetics even if the LDL component is within

normal limits. Hyperglycemia causes increased activity of hepatic lipase that leads to increased clearance of HDL while impaired catabolism of VLDL causes decreased formation of HDL, which is one of the reasons why HDL-C levels are low in type 2 diabetes [12]. The other reasons for lowered HDL are probably most diabetics are obese and may be due to high triglycerides. HDL cholesterol is inversely correlated with cardiovascular risk [13]. Mild hyperglycemia leads to increased LDL production while insulin resistance or relative insulin deficiency causes defects in LDL clearance; thus the LDL cholesterol levels increase. Both dyslipidemia and HbA<sub>1c</sub> are independent risk factors for developing cardiovascular events. Lowering HbA<sub>1c</sub> will certainly lower the risk of having CVD later in life. It has been shown that reducing the HbA<sub>1c</sub> level by 0.2% could lower the mortality by 10% [14]. Is there an effect of age and duration of diabetes on lipid profile is an topic for discussion, nothing has been proved as of now. Some studies report there is clear association while few other studies negate this idea [15,16].

The Atherogenic index of plasma (AIP) has recently been proposed as a marker of plasma atherogenicity and is positively correlated with cardiovascular disease risk[2]. In view of the predisposition for the development of atherosclerotic vascular disease in the diabetics, clinicians give importance to good glycaemic and cholesterol control in the patients. Triglycerides and HDL-cholesterol in AIP reflect the balance between the atherogenic (bad cholesterol) and protective (good cholesterol) lipoproteins. AIP correlates with the size of pro- and antiatherogenic lipoprotein particles. Clinical studies have shown that AIP predicts cardiovascular risk. AIP reflects the delicate metabolic interactions within the whole lipoprotein complex[17].

So what is the target HbA<sub>1c</sub>? Lowering A1C to below or around 7% as already been said it reduces both microvascular as well as macrovascular complications of diabetes. So, clinician should be advising patients to keep

**Case Report**

their HbA1c levels below 7% (in a non-pregnant adults). In gestational pregnancy the the HbA1c target is around 6%. Less stringent HbA1c goals (<8%) in patients with a history of severe hypoglycemia, has limited life expectancy, advanced microvascular or macrovascular complications, hypoglycaemia unawareness and extensive comorbid conditions and in those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education (DSME), and effective doses of multiple glucose-lowering agents including insulin[18].

**Conclusion**

These findings clearly indicate that HbA1c can provide valuable supplementary information about the extent of atherogenic dyslipidemia, Atherogenic Index of Plasma, besides its primary role in monitoring long-term glycemic control. Therefore, regular screening for HbA1c estimation can help in clinical management to prevent complications by achieving adequate glycemic control. Thus, HbA1c can be used as a potential biomarker to identify patients with cardiovascular risk and patients with incipient nephropathy in Type 2 Diabetes Mellitus.

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