Original Article

# HBA1C: PREDICTOR OF DYSLIPIDEMIA AND ATHEROGENICITY IN DIABETES MELLITUS

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## ABSTRACT

Objective: This study was done to evaluate the diagnostic value of Glycated hemoglobin (HbA1c) in predicting diabetic dyslipidemia and atherogenicity.

Method: The study consisted of 70 male patients of type 2 diabetes mellitus of age between 45 - 50, duration more than 5 years. The patients were classified into two groups depending on their glycated hemoglobin (HbA1c); Good Glycemic Control (GGC) group having HbA1c < 7.0% (n= 35) and Poor Glycemic Control (PGC) group having HbA1c > 7.0% (n= 35). Dyslipidemia was defined as per the National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III guidelines. Standard tests were used to analyze Fasting blood glucose level (FBSL), Glycated hemoglobin level (HbA1c) and serum Lipid Profile: Triglyceride (TG), Total Cholesterol (TCH), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL). While Atherogenic Index of Plasma (AIP) was calculated by standard formula (base 10 logarithm of the ratio of TG to HDL).

Statistical analysis was done by Z test using Microsoft Office Excel 2010.

Results: HbA1c showed direct correlation with FBSL, TG, TCH, LDL and AIP while there was inverse correlation with HDL. Statistically significant 'p' values were obtained for FBSL, TG, LDL and AIP. While that for TCH and HDL was not significant.

Conclusion: These findings clearly indicate that HbA1c can provide valuable supplementary information about the extent of circulating lipids and AIP besides its primary role in monitoring long-term glycemic control. Thus, HbA1c can be used as a predictor of cardiovascular risk in diabetics.


## INTRODUCTION

Epidemiological studies have demonstrated that type 2 diabetes mellitus (DM) is a well-known risk factor for the development of cardiovascular disease, cerebrovascular disease, and peripheral vascular diseases. Alterations in lipid and lipoprotein profile contribute to artherosclerosis in type 2 diabetes. [1]

Diabetic dyslipidemia is generally characterized by increased plasma triglyceride (TG) and decreased high-density lipoprotein cholesterol (HDL-C) concentrations, a preponderance of small, dense low-density lipoprotein (LDL), and an increased apolipoprotein B concentration. Although the major focus on the connection between lipids and CHD is on LDL-cholesterol (LDL-C), the Adult Treatment Panel III has recognized the important roles of HDL-C and TGs, calling this combination an atherogenic dyslipidemia. [2]

Several lipoprotein-related indices [plasma concentrations of lipids (LDL-C, HDL-C, and TGs), molar ratios (TG/HDL-C and LDL-C/HDL-C), and particle size (LDL and HDL)] have been used to predict CHD risk. The total cholesterol/HDL-C and LDL-C/HDL-C molar ratios have good predictive value for future cardiovascular events. Another molar ratio, log TG/HDL-C popularly

known as Atherogenic Index of Plasma (AIP), is also a significant independent predictor of CHD. [2]

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. 15 AIP's significance as a marker is based on the following facts: it is found increased in cohorts at high risk for CAD; it is positively correlated with the fractional esterification rate of HDL-C (FERHDL), which is perhaps the most dependable marker for the atherogenic capacity of the lipid-lipoprotein profile; and it is inversely correlated to LDL-C

particle size (an indirect indicator of LDL particle size). [16]

The amount of glycated hemoglobin (HbA1c) reflects the glycemic control of a patient during the 6 – 8 week period before the blood sample was obtained. The amount of HbA1c correlates well with fasting and postprandial blood glucose levels. At present HbA1c is the best surrogate marker we have for setting goals of treatment. 5 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. [6]

## OBJECTIVE

This study was done to evaluate the diagnostic value of Glycated hemoglobin (HbA1c) in predicting diabetic dyslipidemia and atherogenicity.

## MATERIAL AND METHODS

This study was conducted at Dr. Milind Patwardhan's Endocrine Clinic, Miraj between January – June 2011. Informed consent of the patients was taken for the study. The study consisted of 70 male patients of type 2 diabetes mellitus of age between 45 - 50, having duration of illness more than 5 years. All patients underwent clinical examination and those with abnormal liver function, nephropathy, neuropathy or retinopathy were excluded from the study.

The patients were classified into two groups depending on their glycated hemoglobin (HbA1c); Good Glycemic Control (GGC) group having HbA1c < 7.0% (n= 35) and Poor Glycemic Control (PGC) group having HbA1c > 7.0% (n= 35).

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 by presence of one or more than one abnormal serum lipid concentration. [6]

Standard tests were used to analyze various parameters- blood samples were collected by standard procedure after overnight fast.

1. HbA1c – estimated using Direct Enzymatic Assay method. [7]
2. FBSL - Glucose oxidase method commonly known as the GOD-PAP (End-Point) method. [9]
3. TG – by Enzymatic colorimetric (End point) method. [10]
4. TCH - by Enzymatic colorimetric (End point) method. [11,12]
5. LDL & HDL - by precipitation method using a reagent that consists of modified polyvinyl sulfonic acid (PVS) and polyethylene-glycol methyl ether (PEGME). [13]
6. AIP – derived by formula: base 10 logarithm of the ratio of TG to HDL. [3,4]

Statistical analysis was done by Z test using Microsoft Office Excel 2010.

| Parameter (n = 70) | Mean ± SEM | Correlati-on with HbA1c | Inference |
|---|---|---|---|
| HbA1c | 7.53 ± 0.27 | - | - |
| FBSL | 143.84 ± 4.89 | 0.81 | Direct |
| TG | 152.66 ± 6.96 | 0.40 | Direct |
| TCH | 176.55 ± 4.54 | 0.26 | Direct |
| LDL | 107.02 ± 4.49 | 0.31 | Direct |
| HDL | 37.96 ± 1.06 | - 0.19 | Inverse |
| AIP | 0.21 ± 0.01 | 0.34 | Direct |

Table 1: Correlation of HbA1c levels with other parameters:-

Thus, direct correlation of HbA1c was observed with FBSL, TG, TCH, LDL and AIP. While inverse correlation was observed between HbA1c and HDL.

| Glycated Hemoglobin (HbA1c) | | | |
|---|---|---|---|
| Parameter | PGC group (n=35) | GGC group (n=35) | P-value |
| FBSL | 173.46 ± 5.88 | 114.22 ± 3.31 | <0.0001** |
| TG | 170.05 ± 12.25 | 135.28 ± 5.37 | 0.0094* |
| TC | 185.16 ± 8.09 | 167.95 ± 3.76 | 0.0538 |
| LDL | 118.5 ± 7.51 | 95.54 ± 4.21 | 0.0077* |
| HDL | 36.45 ± 1.55 | 39.46 ± 1.43 | 0.1555 |
| AIP | 0.29 ± 0.035 | 0.17 ± 0.024 | 0.0046* |

**Table 2: Biochemical Parameters categorized by patients' glycemic control (HbA1c):-**

*Statistically significant
**Statistically highly significant

Thus, Statistically highly significant 'p' values were obtained for FBSL and statistically significant 'p' values TG, LDL and AIP in PGC group. While that for TCH and HDL were statistically not significant.

## DISCUSSION

In normoglycemic subjects, a carbohydrate moiety is attached to a small proportion of hemoglobin A, thus creating what is called as glycosylated or glycated hemoglobin. It has three distinct fractions: A1a, A1b and A1c. The A1c fraction accounts for 60% of bound glucose. Nondiabetic individuals have HbA1c values in the range of 3 - 6%. [5]

In conditions of sustained hyperglycemia, such as in diabetes mellitus, the proportion of hemoglobin that is glycosylated increases substantially. This glycosylation is the result of postprandial modification of hemoglobin A molecules; the binding of glucose is a non-enzymatic process that occurs continuously during the life of the red blood cell. Thus the amount of glycated hemoglobin reflects the glycemic control of a patient during the 6 – 8 week period before the blood sample was obtained, given the average life span of red blood cells of 120 days. The amount of glycated hemoglobin correlates well with fasting and postprandial blood glucose levels. At present HbA1c is the best surrogate marker we have for setting goals of treatment. [5]

The diabetic dyslipidemia is associated with elevated triglycerides, LDL and decreased HDL cholesterol. [13]

Hypertriglyceridemia is the most common alteration of lipoproteins in type 2 diabetes. It is caused by hyperglycemia and insulin resistance that together lead to: (1) Overproduction of VLDL triglyceride (2) Defective clearance of VLDL triglyceride, (3) Decreased activity of lipoprotein lipase and (4) Decreased production of apolipoprotein B. Also the composition of VLDL is altered such that the proportion of cholesterol increases and this increases the propensity for atherosclerosis. [14]

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. Again the composition of this LDL is altered in type 2 diabetes such that a good proportion of small dense, triglyceride-enriched LDL is formed. This small dense LDL particle has increased susceptibility for oxidization and plays a major role in atherosclerotic process

because it is easily recognized by macrophages. Also the non-enzymatic glycation of LDL in mild hyperglycemia increases the atherogenic risk. [14]

Hyperglycemia causes increased activity of hepatic lipase that leads to increased clearance of HDL while impaired catabolism of VLDL causes decreased formation of HDL. Thus the HDL levels decrease in type 2 diabetes. [14]

Severity of dyslipidemia increases in patients with higher HbA1c value. As elevated HbA1c and dyslipidemia are independent risk factors of cardiovascular disorders (CVD), diabetic patients with elevated HbA1c and dyslipidemia can be considered as 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%. [6]

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. [6]

Triglycerides and HDL-cholesterol in AIP reflect the balance between the atherogenic and protective lipoproteins. AIP correlates with the size of pro- and antiatherogenic lipoprotein particles. Clinical studies have shown that AIP predicts cardiovascular risk. AIP is an easily available cardiovascular risk marker and an useful measure of response to treatment: AIP < 0.11 → low risk; AIP 0.11 – 0.21 → intermediate risk; AIP > 0.21 → increased risk. 3,4

Significant and positive correlation of HbA1c with AIP indicates that HbA1c can also be used as a potential biomarker for predicting atherogenicity in patients with type 2 diabetes.

The correlation of HbA1c with TCH and inverse correlation with HDL was statistically not significant, the possible cause could be relatively short sample size. Hence, a further study with greater sample size is advised.

## LIMITATIONS

- ❖ We studied a high-risk subset of patients, who attended the endocrine clinic.
- ❖ We compared only lipid variables, and did not take into account the current use of medication or the inflammatory state of the patients.
- ❖ Study group was small

## CONCLUSION

These findings clearly indicate that HbA1c can provide valuable supplementary information about the extent of circulating lipids and AIP besides its primary role in monitoring long-term glycemic control. Thus, HbA1c can be used as a predictor of cardiovascular risk in diabetics. However further study with greater sample size is warranted.

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