

# Study on Correlations Between Glycated Haemoglobin, Lipid Profiles and Blood Glucose Levels in Type 2 Diabetics Living at Moderate High Altitude

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## ABSTRACT

**Introduction:** The study was conducted to look for the effects of polycythaemia on Glycosylated Haemoglobin (GHb) levels and to see the correlations between the levels of haemoglobin, GHb, blood glucose, and lipid profiles including Atherogenic Index of plasma (AIP), in type 2 diabetics living 5800ft above sea level at Gangtok in Sikkim, India. GHb is used to predict the risk of long term complications of Diabetes mellitus (DM) like coronary artery disease (CAD). **Materials and Methods:** The study group consisted of Group I (Type 2 DM male patients with PPG levels <200mg/dl), Group II (Type 2 DM male patients with PPG levels >200mg/dl) and age matched healthy males formed the control group. **Results:** In Group I, GHb levels correlated positively with AIP, but not with TC/HDL-C ratio. In Group II, both PPG and GHb levels correlated positively with Total cholesterol (TC), LDL Cholesterol, TC /HDL-C ratio and AIP. This shows that higher PPG levels are associated with more Atherogenic lipid profiles. Study also showed higher GHb levels in controls at 7.61%, and correlated positively with postprandial glucose (PPG) levels ( $r = 0.92$ ). **Conclusion:** In predicting risk for future CAD, PPG levels and AIP can be used as an adjunct parameter.

**KEYWORDS:** Altitude, atherogenic index of plasma, glycosylated haemoglobin

## INTRODUCTION

Diabetes mellitus is a systemic disease characterized by hyperglycaemia and the development of irreversible, invalidating and often mortal complications.<sup>1</sup> With over 20 million diabetic subjects, India leads the world in the number of individuals with diabetes.<sup>2</sup> India has thus become the “Diabetic Capital of the World”.<sup>3</sup>

Of all the complications that beset diabetic subjects, the most dangerous and life threatening is coronary artery disease (CAD). Diabetic subjects have two or more folds higher risk for CAD compared to non-diabetic population.<sup>4</sup> Despite the wide geographical variation in the prevalence of diabetes and CAD, the association of these two remains strong. Irrespective of the ethnic background, diabetic subjects have been shown to have high risk for CAD compared to the

non-diabetic population.<sup>5</sup> Several landmark studies in the west have revealed a strong association of CAD with plasma glucose levels.<sup>6-8</sup> Chennai Urban Population Study which has been done in India has revealed that both fasting plasma glucose (FG) and 2 hr post prandial plasma glucose (PPG) levels are strongly associated with CAD.<sup>9</sup>

### Diabetes Mellitus and Glycohaemoglobin

Glycohaemoglobin (GHb, glycated haemoglobin, glycosylated haemoglobin) is a generic term for haemoglobin bound irreversibly (ketoamine form) to glucose. Total glycated haemoglobin (Total GHb) refers to all the glycated haemoglobins, including glycated haemoglobin variants. A1c is the nonenzymatic glycated product of the haemoglobin beta-chain at the valine terminal residue. The number 1c following HbA represents the order in which this haemoglobin is detected on chromatography. Hence, other haemoglobin peaks are referred to as HbA1a1, HbA1a2, HbA1b, and so forth.<sup>10</sup> The A1c constitutes about 60-80% of total glycated haemoglobin. It is normally present, albeit at low levels, in circulating red cells because of the glycosylation reaction between haemoglobin and circulating glucose.<sup>11</sup>

In the presence of excess plasma glucose, the haemo-

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globin beta-chain becomes increasingly glycosylated, making the A1c a useful best indicator of glycaemia.<sup>2</sup> The importance of A1c as an index of diabetes control was reinforced by the Diabetes Control and Complications Trial (DCCT).<sup>12</sup> This study demonstrated a direct correlation between glycemic control as indicated by A1c and the likelihood of developing long-term diabetes-related complications. Current clinical recommendations of the American Diabetes Association suggest that GHb be maintained at 7%, consistent with a decreased risk for developing long-term complications from diabetes mellitus.<sup>13</sup> A reevaluation of the treatment regimen should be undertaken in patients with repeated GHb values >8%.<sup>14</sup> Because GHb is based on haemoglobin, both qualitative and quantitative variations in haemoglobin can affect the GHb value. These factors need to be considered when interpreting GHb results and serve to limit the use of GHb as a diagnostic test for diabetes.

### Diabetes Mellitus and Dyslipidaemia

In diabetes, there is a derangement in the metabolism of lipids and fat, which leads to abnormal serum lipid pattern. Dyslipidaemia has long been shown to have a strong relation with CAD.<sup>2</sup> Type 2 diabetic patients have markedly increased risk of CAD than similarly dyslipidaemic non diabetic subjects.<sup>15</sup> Low HDL Cholesterol, high LDL cholesterol, and high total and VLDL triglycerides, high Total cholesterol to HDL cholesterol (TC/HDL-C) ratio, are powerful risk indicators for coronary heart disease events in patients with type 2 diabetes mellitus.<sup>16,17</sup>

The Atherogenic Index of Plasma (AIP) has recently been proposed as a marker of plasma atherogenicity because it is increased in people at higher risk for coronary heart disease and is inversely correlated with LDL particle size.<sup>18</sup> AIP is calculated as  $\log(TG/HDL-C)$ , with TG and HDL-C expressed in molar concentrations.<sup>19</sup> Previous studies suggest that AIP values of -0.3 to 0.1 are associated with low CAD risk, 0.1 to 0.24 medium and above 0.24 high risk. AIP can be easily calculated from standard lipid profile. As a marker of lipoprotein particle size it adds predictive value beyond that of the individual lipids, and/or TC/HDL-C ratio.<sup>20</sup>

### Diabetes Mellitus, GHb, Lipid profiles, and Altitude

Human physiology is affected in different ways at high altitude. Some studies on non-diabetic subjects at altitude show an increase in fasting glucose and counter-regulatory hormones although other factors like acclimatization or time at altitude modify this rise, but the effect of altitude on diabetes mellitus is unknown.<sup>21-23</sup> In people who are acclimatized to living at high altitudes, there is an increase in the number of erythrocytes, and consequently an increase in the whole blood total haemoglobin concentration. Individual GHb values can be influenced by polycythaemia and this might result in a wrong diagnostic classification of the involved patient and cause unnecessary

therapeutic interventions.<sup>24</sup>

Moreover, the lower mortality from coronary ischemic disease in populations living at high altitude has been related to an increase of HDL-cholesterol at altitude.<sup>25</sup> Higher levels of serum HDL have been detected in those who live at high altitudes, and increases in HDL have been observed in a population migrating from lower altitudes to high mountain regions.<sup>26-29</sup> Previous studies indicate that HDL cholesterol levels are linearly and significantly increased when living at a higher altitude. This fact should be taken into account when comparing cardiovascular risk in populations living at different altitudes.<sup>25</sup>

Keeping this background in mind, the study was designed to see the correlations between blood glucose levels, haemoglobin levels, glycosylated haemoglobin levels, and lipid profiles including AIP, in Type 2 diabetic patients residing at Gangtok. Gangtok is in the state of Sikkim in India and at an altitude of 5800 ft (1780m) above sea level.

### MATERIALS AND METHODS

A cross sectional, convenience sample study was carried out over a period of six months in the out patients department of Central Referral Hospital, Gangtok and during this period, a total of 33 male patients with type 2 diabetes, who met the inclusion criteria were selected. The inclusion criteria were as follows: Male patients aged between 40 and 60 years, who were freshly diagnosed with type 2 diabetes, and were living in the Gangtok for a minimum period of one year, prior to the study, and were willing to participate in the study. Diabetic patients who were taking hypoglycaemic drugs were excluded as these drugs might effect the plasma lipid profile in these patients.<sup>30</sup> Ten healthy individuals of the same age and gender, who volunteered, formed the control group. All the selected patients and controls were natives of Gangtok. Only male patients were selected to minimize gender bias on haemoglobin levels.

Fasting blood sample and Post prandial blood samples were obtained by venipuncture from all the selected patients and controls after taking informed consent. Fasting blood sample was used for the estimation of Fasting plasma glucose (FG), Haemoglobin, GHb and lipid profile namely Total Cholesterol (TC), Triglycerides (TG), HDL-Cholesterol (HDL-C) and LDL-Cholesterol (LDL-C), TC/HDL-C ratio, AIP were calculated. Postprandial blood samples were used for the estimation of Postprandial Glucose levels (PPG).

Based on the postprandial glucose levels, the subjects were divided into three groups as follows:

- Control (PPG <140mg/dl) (n=10)
- Group I (PPG <160-200 mg/dl) (n=14)
- Group II (PPG >200mg/dl) (n=19)

Plasma Glucose both in the fasting and the post prandial samples were estimated by enzymatic - glucose

oxidase-peroxidase method using commercially available kits.<sup>31</sup> Haemoglobin was estimated by cyanmethaemoglobin method using whole blood samples.<sup>32</sup> Total GHb was estimated using the cation-exchange resin kits.<sup>33</sup> The procedure can be described briefly as follows: a hemolysed preparation of the whole blood is mixed continuously for 5 minutes with a weak binding cation-exchange resin. During this time, non-glycosylated haemoglobin binds to the resin. After the mixing period, a filter is used to separate the supernatant containing the glycohaemoglobin from the resin. The percentage glycohaemoglobin is determined by measuring the absorbance at 415nm of the glycohaemoglobin fraction and the total haemoglobin fraction. The ratio of the two absorbencies gives the percent total GHb.

Serum was used for the estimation of Total Cholesterol,<sup>34</sup> Triglyceride,<sup>35</sup> and HDL-Cholesterol by enzymatic methods.<sup>36</sup> LDL-Cholesterol was calculated by using the Friedewald equation<sup>37</sup>. The ratio of TC to HDL-C was also calculated. AIP was calculated as log (TG/HDL-C), with TG and HDL-C expressed in molar concentrations<sup>19</sup>.

#### Statistical analysis

The laboratory results were statistically analyzed using SPSS software package. Student t-test was used for comparison of the groups with the control. P values <0.05 were considered significant at 5% level. The Pearson's correlation coefficient (r) was calculated to look for correlations between different parameters within the groups and with the control group.

#### RESULTS

Age, blood glucose, Hb, Ghb values of different study groups are presented in Table I. The FG and PPG levels were significantly higher in both the groups when compared to the controls. GHb values in the control group were slightly higher (at 7.61% ±0.47) than the suggested normal value of 7 % given by the American Diabetic Association<sup>13</sup>. GHb values were significantly more in group 2 than controls. In Group 2, the GHb levels correlated positively with PPG levels (r = 0.92, p <0.001).

Table II gives the lipid profile in different study groups. Total Triglyceride levels, the ratio of TC/ HDL- C and AIP were significantly more in Group 2 when compared to the control group. HDL-cholesterol levels were significantly lower in Group 2 when compared to controls.

The analysis for correlations between glucose levels and lipid profiles show, in Group 1, GHb levels correlated positively with Triglycerides (r = 0.65, p<0.01) and AIP (r= 0.62, p <0.01). In Group 2, PPG levels and GHb levels correlated positively with Total cholesterol, LDL cholesterol, TC/HDL-C ratio and AIP (Table III).

Though previous studies have shown that people living

at higher altitudes have higher levels of HDL- Cholesterol, such a finding is not seen in the present study.

Table I. Glucose, Haemoglobin and GHb levels

	Control (n=10)	Group 1 (n=14)	Group 2 (n=19)
AGE (yrs)	48.77 ±6.3	50.8 ±7.05	51.45 ±7.65
FG (mg/dl)	76.8 ±9.3	110.2 ±14.29*	123.21 ±17.46*
PPG (mg/dl)	113.7 ±10.66	176.4 ±12.55*	266.89 ±59.72*
Hb (mg/dl)	14.66 ±0.86	14.81 ±0.96	14.69 ±0.91
GHb(%)	7.61 ±0.47	8.25 ±0.52	10.24 ±0.80*

\* P value < 0.05- Significant

Table II. Fasting Lipid Profiles

	Control (n=10)	Group 1 (n=14)	Group 2 (n=19)
Total Cholesterol (TC) (mg/dl)	158.9 ± 13.1	164.79 ± 14.5	190.16 ± 30.0
Total Triglycerides (mg/dl)	93.2 ± 16.07	101.07 ± 17.4	127.95 ± 23.96*
HDL - Cholesterol (HDL-C) (mg/dl)	43.3 ± 2.2	39.71 ± 3.02	36.18 ± 2.7*
LDL - Cholesterol (mg/dl)	96.96 ± 15.64	104.86 ± 13.76	128.38 ± 28.1
TC/ HDL-C ratio	3.68 ± 0.38	4.16 ± 0.38	5.62 ± 0.91*
AIP	-0.045 ± 0.03	0.03 ± 0.097	0.17 ± 0.1*

\* P value <0.05 -Significant

Table III. Correlation values between PPG, GHb with lipid profiles in Group 2

	Total cholesterol	LDL- Cholesterol	TC/HDL- C ratio	AIP
PPG	r=0.84 p<0.001	r=0.85 p<0.001	r= 0.86 p<0.001	r=0.46 p<0.05
GHb	r=0.73 p<0.001	r= 0.76 p<0.001	r=0.73 p<0.001	r= 0.46 p<0.05



## DISCUSSION

In clinical practise, the clinician usually compares the reported values with the reference values for interpreting a patient's laboratory result, but the reference values are not specific to where they live.<sup>38-41</sup> Unfortunately reference values are obtained only from a population predominantly living in North America and Europe and not from all over the world population.<sup>42</sup> In the present study, the haemoglobin levels were on the higher side of normal haemoglobin levels in all the groups, in accordance with the altitude they were staying. It has been reported that up to moderate high altitudes, an adaptation mechanism causes increasingly higher numbers of red blood cell and consequently higher haemoglobin production.<sup>43,44</sup> The reason for this has been attributed to the altitude-induced decrease in partial pressure of oxygen, which leads to a drop in renal tissue oxygenation. It is hypothesized that this reduction in renal tissue oxygenation stimulates the synthesis and release of erythropoietin (EPO), the principal hormone that regulates erythrocyte (RBC) and haemoglobin production. In turn, an increase in serum EPO concentration stimulates the synthesis of new RBCs in the red bone marrow and also synthesis of heme and haemoglobin.<sup>45,46</sup>

Because of the quantitative increase in haemoglobin concentrations, there was observed concomitant increase in GHb levels above the reference range even in the control group. This suggests that GHb values can be affected by factors other than of glycaemia. Taking this into consideration laboratories should develop their own reference ranges for GHb, especially in places at higher altitudes. In the present study, significant positive correlation was seen between PPG levels and GHb but it correlated less with FG levels in both the groups. This is similar to findings in Diabetes Control and Complications Trial (DCCT) research group in which GHb levels correlated more with Mean plasma glucose and correlated less with FG levels.<sup>14,47</sup> This means Fasting PG should be used with caution as a surrogate measure of mean plasma glucose levels. The PPG levels also correlated positively with Total Cholesterol, LDL-Cholesterol, TC/HDL-C ratio and AIP in Group II. Since Group II consists of patients with PPG levels more than 200mg/dl, it suggests that higher PPG levels are associated with more atherogenic lipid profiles. This should be remembered while formulating treatment plans and it might be necessary to target the PPG levels also in addition to FG levels. Many investigators have noted a strong correlation between GHb levels of diabetics with lipids and lipoproteins, but not with HDL cholesterol.<sup>48</sup> In this study GHb, correlated positively with Triglycerides and AIP in Group I. In Group II, GHb levels correlated positively with Total cholesterol, LDL-Cholesterol, TC/HDL-C ratio and AIP. Since in the calculation of AIP, the Triglyceride levels are also considered, it may prove to be a more valuable adjunct while calculating the overall risk of diabetics for future CAD.

## CONCLUSION

The study points out the importance of each lab establishing its own reference ranges, or if possible to establish the reference range with respect to the altitude. The study shows that there is a need to consider, not only fasting, but also the post prandial glucose levels while formulating treatment plans, as higher PPG levels are associated with more Atherogenic lipid profiles. The study also emphasizes the usefulness of Atherogenic Index of Plasma in calculating the risk of complications associated with diabetes mellitus.

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