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RESEARCH ARTICLE

CONTRIBUTION OF FASTING AND POSTPRANDIAL BLOOD GLUCOSE TOWARDS GLYCATION OF HEMOGLOBIN IN PREDIABETES

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ABSTRACT

Background: Prediabetes is a stage in the natural history of disordered glucose metabolism rather than a distinctive clinical entity representing an interim condition and a risk factor for the development of diabetes along with an increase in cardiovascular and microvascular complications. So, prediabetes is a state of nondiabetic hyperglycemia that does not satisfy the diagnostic criteria for diabetes mellitus. **Objectives:** To correlate the levels of fasting blood glucose (FBG) and postprandial blood glucose (PPBG) with glycated hemoglobin (HbA_{1c}) in prediabetics. **Materials & Methods:** The present case control study was performed at Pt. B. D. Sharma PGIMS, Rohtak includes thirty prediabetes patients of age group 20-40 years diagnosed on the basis of HbA_{1c} (5.7-6.4%). Thirty healthy and age matched control were taken. Venous blood samples were obtained for analysis of fasting blood glucose, postprandial blood glucose and HbA_{1c} after obtaining written consent. Samples were processed by centrifugation and analysed on the same day. **Results:** The correlation coefficient between fasting blood glucose (108.50 ± 10.51 mg/dL) and HbA_{1c} (5.94 ± 0.21%) is r = 0.444 with p value = 0.014 which is lower than the correlation coefficient between postprandial blood glucose (155.33 ± 13.18 mg/dL) and HbA_{1c} i.e r = 0.648 with p value = 0.001. **Conclusion:** The contribution of postprandial blood glucose towards glycation of hemoglobin is more than the contribution of fasting blood glucose levels.

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INTRODUCTION

Prediabetes (preDM) is a state of nondiabetic hyperglycemia that does not satisfy the diagnostic criteria for diabetes mellitus. It is considered that all forms of diabetes pass through this preDM state before escalating into full blown diabetes (Rhee, 2011). Prediabetes is a stage of disordered glucose metabolism rather than a distinct clinical entity and a risk factor for the development of diabetes along with an increase in cardiovascular and microvascular complications. The transition from preDM to diabetes may take years but may also be rapid (Buysschaert, 2011). National prevalence rate of impaired glucose tolerance (IGT) in India was 4.7% in 2015 which is expected to increase to 5.5% by 2040. So by 2040, 63.6 million people will be expected to suffer from IGT in India (International Diabetes Federation, 2015). According to American Diabetes Association (ADA), diagnostic criteria for preDM is (American Diabetes Association, 2014).

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- Impaired fasting glucose (IFG) with fasting plasma glucose levels of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).
- Impaired glucose tolerance (IGT) with plasma glucose levels of 140 to 199 mg/dL (7.8 to 11.0 mmol/L) 2-hour postprandial.
- Glycated hemoglobin (HbA_{1c}) of 5.7 to 6.4%.

In pre DM pathophysiology, it has been found that (I) In IFG, there is reduced heap to renal insulin sensitivity along with impairment in basal insulin secretion and first phase insulin release causing fasting hyperglycemia. (II) In IGT, there is peripheral insulin resistance along with impairment in first and second phase insulin responses which is responsible for postprandial hyperglycemia. (III) In combined IFG and IGT, there is no significant interaction between the two so that the associated defects in insulin secretion and sensitivity is additive. These results thus support the fact that IFG and IGT are distinct metabolic entity (Meyer, 2006). Fasting plasma glucose (FPG) is a commonly used tool in screening of

diabetes. According to ADA, FPG is the preferred test for diagnosing diabetes and preDM because of its ease of use, acceptability to patients and lower cost but it has a random variation as it reflects current glycemic status and requires fasting for at least 8 hours. Glycated hemoglobin (HbA_{1c}) reflects long term glycemic control and is a more accurate and stable measure than FPG levels (Zhang *et al*., 2015). HbA_{1c} is a widely used test to estimate the degree of glycemic control because it can be measured regardless of the food intake and is simpler than FPG. It reflects long term glucose concentrations versus frequently changing glucose levels. Moreover it is closely related to the chronic complications of diabetes (Rhee, 2011). Advantage of HbA_{1c} level is that it can be determined by both FPG and post prandial blood glucose (PPBG) exposure (Jeon *et al*., 2013). HbA_{1c} results from the nonenzymatic, irreversible concentration dependent covalent bonding of glucose to hemoglobin within the erythrocytes. At one end of the paired β chains of normal adult hemoglobin (HbA), there is an available amine group known as the N-terminal valine. So, HbA_{1c} is defined as a molecule of HbA with glucose bound at its N-terminal valine (Hare, 2012). Glycation occurs in a two step Maillard reaction. It involves the initial formation of a labile Schiff base which undergoes a subsequent Amadori rearrangement leading to formation of an Amadori product i.e HbA_{1c} (Derr, 2003). The concentration of HbA_{1c} correlates with the average blood glucose levels over the preceding three months. This relationship is complex due to the diverse age of erythrocytes in circulation at any particular time. An older erythrocyte is more likely to be glycated than a younger one (Nathan, 2008; Jeffcoate , 2004). As a consequence of relationship between glycemia and HbA_{1c}, it is clear that there is a significant association between HbA_{1c} and various clinical outcomes. Moreover, HbA_{1c} is related to the risk of microvascular (in both type 1 and type 2 diabetes) as well as macrovascular (in type 1 diabetes) complications (Zafon *et al*., 2013). It has been found that HbA_{1c} is a predictor of cardiovascular events even in people without diabetes. Improved glycemic control which is indicated by reduction in HbA_{1c} reduces the long term risk of macrovascular complications in people with type 1 diabetes.

HbA_{1c} is not a direct measure of glycemia. In fact, it measures proportion of hemoglobin proteins bounded by glucose, so it is affected by various factors in addition to glucose concentrations. Mainly three well defined conditions alter final HbA_{1c} levels, the amount of glucose entering the erythrocytes, the rate of glycation-deglycation inside the cell and the average erythrocyte lifespan (Hare *et al*., 2012). Any process that reduces the average age of erythrocytes will lower HbA_{1c}, whereas increase in the age of erythrocytes will increase HbA_{1c}. Oxidative stress is a key determinant of glycation rate and elevated oxidative stress is associated with increased HbA_{1c} concentrations in nondiabetic subjects (Selvaraj *et al*., 2006; Sathiyapriya *et al*., 2007). Since HbA_{1c} testing can be performed at any time of day and without any special patient preparation, so it is more convenient for patients and health care providers as compared to oral glucose tolerance test (OGTT) and FPG because fasting is inconvenient and patients do not fast properly leading to misdiagnosed diabetes. HbA_{1c} can be measured regardless of the length of fast or the content of the previous meal. HbA_{1c} is a more comprehensive means of total glycemic exposure than FPG because it measures plasma glucose in fasting state as well as in the postprandial state. Hence it may be a better predictor of glycemia related complications (Rohlfing, 2000).

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with Department of Medicine, Pt. B. D. Sharma PGIMS, Rohtak. In the present study, 30 patients of age group between 20-40 years were enrolled as cases based on HbA_{1c}. 30 healthy and age matched individuals were enrolled as controls.

Inclusion criteria: Patients of age group between 20-40 years satisfying the criteria of prediabetes on the basis of HbA_{1c} (5.7 to 6.4%) were included in the study.

Exclusion criteria: Patients with hemoglobin < 9 gm% and any history suggestive of hemoglobinopathies.

- Patients with history suggestive of endocrine disorders like thyroid, adrenal and pituitary glands disorders.
- Patients with history suggestive of any drug intake affecting glucose metabolism.

Sample Collection

After getting written consent from the cases and controls, detailed history was taken and recorded in their respective proforma. Six mL of venous blood sample was taken from the antecubital vein aseptically, out of which:

- For estimation of fasting blood glucose, 2 mL of blood was collected in sodium fluoride vacutainer after fasting of eight hours.
- For estimation of postprandial blood glucose, 2 mL of blood was collected in sodium fluoride vacutainer. Sample was collected 2 hours after taking meals.
- For estimation of HbA_{1c}, 2 mL of blood was collected in EDTA anticoagulant vacutainer.

Samples were processed on the same day of collection. Serum from sodium fluoride vacutainer was separated by centrifugation. The investigations were performed on the RANDOX (Randox Laboratories Limited, UK) by using standard Enzymatic kit methods (Sacks, 2012). HbA_{1c} was determined by turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood (Gene *et al*., 2012).

Statistical Analysis: Primary outcome were calculated by applying Unpaired‘t’ test and secondary outcome were obtained by using two-tailed Pearson correlation between variables of prediabetics cases and controls by using the statistical package (IBM SPSS 20). Data were considered to be significant if $p < 0.05$ and highly significant with $p < 0.001$.

RESULTS AND OBSERVATIONS

In the present study, it was observed that out of 30 cases, 21 (70%) had impaired fasting blood glucose while 25 (83.33%) had impaired postprandial blood glucose and 18 (60%) had both impaired fasting and postprandial blood glucose levels. Mean ± SD of fasting blood glucose levels of cases was 108.5 ± 10.51 mg/dL and controls was 89.40 ± 7.15 mg/dL with p value = 0.001 (figure 1). Mean ± SD of postprandial blood glucose levels of cases was 155.33 ± 13.18 mg/dL and controls was 121.23 ± 7.23 mg/dL with p value = 0.001 (figure 2). Mean ± SD of HbA_{1c} in cases was 5.94 ± 0.21% and controls was 5.24 ± 0.32% with p value = 0.001 (figure 3).

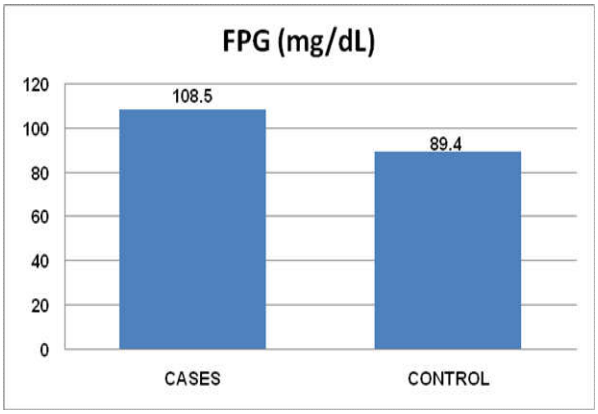

Figure 1. Mean fasting blood glucose levels amongst cases and controls

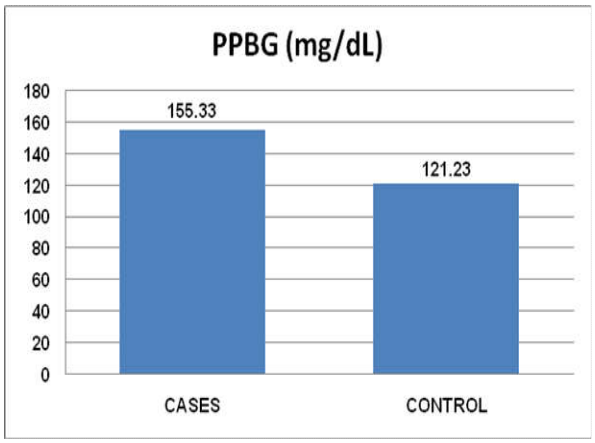

Figure 2. Mean postprandial blood glucose levels amongst cases and controls

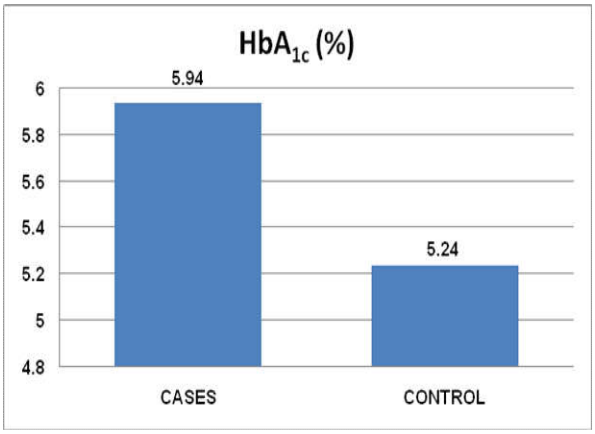

Figure 3. Mean HbA_{1c} levels amongst cases and controls

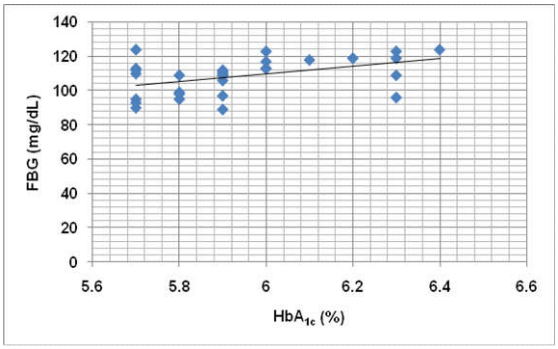

Figure 4. Graph showing the correlation between HbA_{1c} & FBG

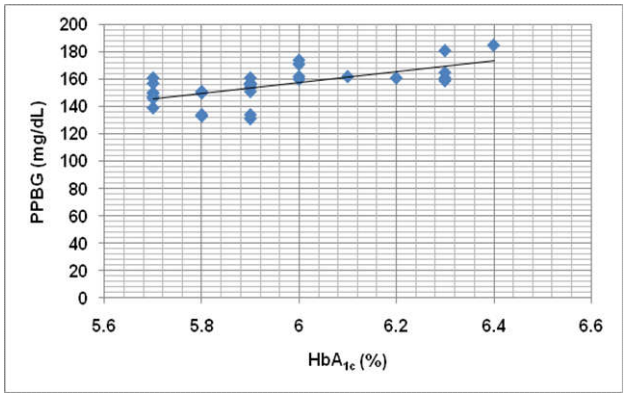

Figure 5. Graph showing the correlation between HbA_{1c} & PPBG

Table 1. Correlation of HbA_{1c} with different parameters

S. No.	Parameters	Correlation Coefficient (r)	p value
1.	HbA_{1c} Vs FBG	0.444	0.014*
2.	HbA_{1c} Vs PPBG	0.648	0.001**

*- significant difference **- highly significant difference

Two-tailed Pearson's correlation between parameters: In the present study, it was found that HbA_{1c} had positive correlation with both fasting and postprandial blood glucose (Table 1 & figure 4 and 5).

DISCUSSION

HbA_{1c} is not a direct measure of glycemia. In fact, it measures proportion of hemoglobin proteins bounded by glucose, so it is affected by various factors in addition to glucose concentrations. Mainly three well defined conditions alter final HbA_{1c} levels, the amount of glucose entering the erythrocytes, the rate of glycation-deglycation inside the cell and the average erythrocyte lifespan (Hare, 2012). HbA_{1c} is a more comprehensive means of total glycemic exposure than FPG because it measures plasma glucose in fasting state as well as in the postprandial state. Hence it may be a better predictor of glycemia related complications (Rohlfing *et al*., 2000). Mean of fasting blood glucose and postprandial blood glucose of cases was significantly higher than controls. Out of 30 cases, 21 (70%) had impaired fasting blood glucose while 25 (83.33%) had impaired postprandial blood glucose and 18 (60%) had both impaired fasting as well as postprandial blood glucose. It was found that HbA_{1c} had positive correlation with FBG and PPBG indicating that PPBG contributes more towards glycation of hemoglobin in comparison to FBG (Table 1). Thus, PPBG predicts better overall glycemic control than FBG. Monnier *et al* also observed that the relative contribution of PPBG decreased progressively from the lowest to the highest quintile of HbA_{1c}. It was observed that postprandial glycemia plays a major role in the metabolic disequilibrium in patients of mild to moderate hyperglycemia in contrast to fasting hyperglycemia which is a main contributor to the overall diurnal hyperglycemia in poorly controlled diabetic patients. So the role of PPBG decreases as patients progress toward poor diabetic control. Moreover, PPBG is a stronger predictor of cardiovascular disease than IFG. Fasting hyperglycemia plays a major role when HbA_{1c} level rises above 8.4%. There is a progressive shift as a continuous spectrum in the respective contributions of PPBG and FBG from fairly to poorly controlled diabetic patients (Monnier *et*

al., 2003). Avignon *et al* also observed that PPBG contributes more towards glycation of hemoglobin in comparison to FBG. It was explained by the fact that FBG correlates positively with hepatic glucose overproduction and negatively with metabolic clearance of glucose. Therefore, improvement in the insulin sensitivity of peripheral tissues and reduction in glucose hepatic overproduction leads to normalization of FBG. PPBG depends on insulin resistance, hepatic glucose output and insulin secretion capacity of the pancreas in response to meals. Postprandial hyperglycemia represents the overall pathophysiological process of the disease like insulin resistance, inadequate suppression of hepatic glucose output and defective insulin response to meals compared to FBG. Moreover, an individual is in the fasting state only during the second part of the night in contrast to postprandial state for the rest of the day.

So, PPBG correlate better than FBG with overall diabetic control which is estimated by HbA_{lc} levels. Therefore, PPBG values should be more widely used in estimating the glycemic control of an individual. So in case of nonavailability for measurement of HbA_{lc}, PPBG is a good additional substitute in evaluating the mean glycemic control of an individual (Avignon, 1997). Rosediani *et al* also observed a positive correlation of FBG & PPBG with HbA_{1c} in diabetics patients and concluded that PPBG correlates better than FBG with HbA_{lc} (Rosediani *et al*., 2006). Our finding is in contrast to study done by Bonora *et al* who observed that HbA_{1c} correlates better to fasting glucose levels than postprandial levels. Moreover, fasting glucose levels were found to be independent predictors of HbA_{1c}. This was explained by the fact that hemoglobin glycation is due to interprandial and nocturnal glucose levels than the glucose spikes after meals. Thus, HbA_{1c} is poor indicator of degree of postprandial glucose control (Bonora *et al*., 2001). Mean glucose level strongly correlate with HbA_{1c} indicating that glycation process is a function of the average glucose exposure.

Conclusion

The contribution of postprandial blood glucose towards glycation of hemoglobin is more than the contribution of fasting blood glucose levels. PPBG correlate better than FBG with overall diabetic control, so serve as a additional substitute in evaluating the mean glycemic control of an individual.

Conflict of interest: There is no area of conflict in the research project.

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