

# Predictive Role of Fasting and Post-Prandial Glucose towards Glycemic Control

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## ABSTRACT

**Introduction:** In the absence of glycated hemoglobin (HbA1c) estimation, particularly in rural set-up in most developing countries, the overall metabolic control may be predicted by evaluating fasting and postprandial plasma glucose (FPG and PPPG).

**Aim:** To evaluate the relative contribution of fasting and postprandial glucose towards glycemic control.

**Materials and Methods:** A retrospective analysis was carried out from lab reports of all adult who were diagnosed with type 2 diabetes and in whom all investigations were carried out in

the same setting.

**Results:** Younger males revealed elevated glycated hemoglobin compared to their female counterpart and older male compeer. Peri menopausal females exhibited highest HbA1c, FPG and PPPG of all. The HbA1c values correlated significantly with FPG and PPPG. However, FPG levels were found to be more reliable in assessing the glycemic index.

**Conclusion:** FPG was conferred to be the key contributor for glycation of hemoglobin and can assess the shift of glycemic status in diabetics early.

**Keywords:** Diabetes mellitus, Glycated hemoglobin, Glycemic status, Plasma glucose levels

## INTRODUCTION

Diabetes mellitus (DM) is regarded as an emerging pandemic. As per WHO (World Health Organization) fact sheet No 312 (Jan 2015), the global prevalence of DM in 2014 was estimated to be 9% in adults. It led to 1.5 million deaths in 2012, of which 80% deaths occurred in developing countries [1]. In India, about 69 million cases of DM have been diagnosed. It is predicted that by 2040, India will top the rank with 123 million diabetic individuals [2,3]. Incidence of DM in one geographical area differs from other. Few studies have estimated a low (one-fourth) prevalence of diabetes in rural population as compared to the urban community. A recent study by Indian Council of Medical Research (ICMR) estimated a prevalence of 5.3% – 13.6% in different zones of India [4].

Type 2 Diabetes Mellitus (T2DM) affect 90% of individuals with diabetes worldwide and is influenced by synergistic effects of greater longevity, excessive body weight and lack of physical activity. The usual symptoms of polyuria (excessive urination), polydipsia (excessive thirst), polyphagia (urge to eat all the time), weight loss and fatigue are not very marked. Hence, the diagnoses remain neglected for a longer duration until the complications arises. The consequences commonly encountered with DM are associated with micro- and macro-vascular complications like myocardial infarction, stroke, neuropathy, retinopathy and kidney failure [5]. These sequels are ascribed to various metabolic and structural derangements

implicated by the Advanced glycation end products (AGE), aberrant signaling cascades like Protein Kinase C (PKC) and high reactive oxygen species (ROS) production [6]. The vascular phenomena are direct repercussion of chronic hyperglycemia imputed to inadequate glycemic control and duration of diabetes ( $\geq 5$  years) [7,8]. Early onset of these complications in Indian diabetics has been attributed to poor glycemic control which in turn is reflected by the increasing burden of obesity [2].

Type 2 DM, once appertain as disease of middle and old age. However, evidences are suggestive enough to evince the recent demographic shift that reveal the rising trend of diabetes type 2 in younger cohorts [9,10]. Metabolic control in young diabetic individuals is currently an emerging therapeutic challenge for the diabetes care team [11]. This group represents an aggressive phenotype for obesity, inadequate glycemic control and rapid progression of disease process than their adult partners [12]. Youngsters usually have a higher glycated hemoglobin (HbA1c) levels when compared to older people.

Recent studies have limned a reduction by 30-35% in microvascular complications and 14 -16% in macrovascular consequences when HbA1c values fall off by 1%. The Diabetes Control and Complication Trial (DCCT) study interpreted, 35% reduction for retinopathy and 25-44% reduction for nephropathy for a stable 10% decrease of HbA1c [13]. The group also evaluated for a target mean value

of HbA1c of approximately 7% to be achieved by intensive diabetes therapy and that early intervention can significantly lessen the vascular sequelae [14].

As per ADA (American Diabetes Association), [15] the glycemic recommendation for non-pregnant adults with diabetes is:

- i. HbA1c = <7.0% (53 mmol/L).
- ii. Fasting capillary plasma glucose = 80 – 130mg/dl (4.4-7.2 mmol/L).
- iii. Post prandial plasma capillary glucose = <180mg/dl (<10.0 mmol/L).

HbA1c is the gold standard for assessment of glycemic control. However, clinical scenarios of hemoglobin related disorders like thalassaemia and sickle cell disease, iron deficiency anemia and use of certain drugs such as primaquine in G6PD (Glucose 6-phosphate dehydrogenase) deficient persons, may result in erroneous glycated hemoglobin values. Use of different assays and test standardization protocols, limit its expediency for screening. Besides clinical condition and test protocol, requisite of costly equipments for HbA1c analysis, raises the cost burden to the population. Thus, further restrain the practicability of the test in all laboratories particularly in remote rural areas [16]. Hence, evaluating alternative indices may be pivotal to appraise the glycemic control in such areas. HbA1c values speculate the average blood glucose status over a period of 8 -12 weeks. However, controversies still persist to the fact whether fasting or postprandial blood glucose is the major contributor for glycated hemoglobin. Several studies have been carried worldwide to set forth the fact, but with varied outcome. It is worthy to delve into the significance of correlation of fasting and postprandial plasma glucose to glycated hemoglobin in our community that would aid, to assess whether glycemic targets are being attained in areas constrained for HbA1c detection.

The aim of our study is to evaluate the relative contribution of fasting and postprandial glucose towards glycated hemoglobin and assess the predictive role of fasting and post prandial glucose towards glycemic control.

## MATERIALS AND METHODS

It was a retrospective analysis in which lab records over past six months from September 2015–February 2016 of all diabetic adults who were investigated at the Clinical Chemistry Laboratory, in our hospital at Raipur, India were scrutinized for the study. Of a total of 2137 reports, a total of 472 cases were chosen whose fasting (FPG), postprandial (PPPG) plasma glucose and HbA1c were investigated at the same setting.

### Inclusion Criteria

1. All adult patients who are diagnosed for diabetes.
2. All clinical details and lab reports should be on record.
3. The FPG, PPPG and HbA1c must have been investigated the same day.

### Exclusion Criteria

1. Undiagnosed diabetic cases even if have high FPG or PPPG for the first time.
2. Incomplete clinical details and lab records.
3. Those who were either of FPG, PPPG or HbA1c are not done the same day.

The FPG and PPPG were analyzed in autoanalyzer by glucose oxidase peroxidase method in BA400 (Biosystems Ltd) and HbA1c levels were measured High Performance Liquid Chromatography method in D-10 (Biorad) instrument.

The study group was categorized as per their age:-

Group I- < 45 years

Group II - ≥ 45 years

Age group limitation was defined at 45 years to segregate the population based on perimenopausal age group of females.

To analyze the influence of duration of diabetes on glycemic control, the patients were categorized as those ≤ 5 years and > 5 years taking into consideration the average duration of group I and II patients.

## STATISTICAL ANALYSIS

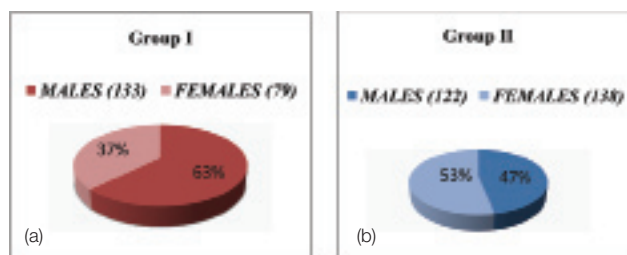
All data were represented as mean ± SD. Statistical analysis was carried using data analysis in Microsoft excel. Kruskal-Wallis and Anova were used to compare non-parametric and parametric data respectively. Linear regression analysis was used for correlation studies. The p-value of < 0.05 was accounted for statistically significant.

## RESULT

As depicted in [Table/Fig-1], percentage of males was higher (63%) than the females in young diabetic group whereas in group II female percentage (53%) was observed to be more. The number of female diabetics in group II were about 75% more than those in group I.

The mean ± SD values of different variables in the study population have been outlined in [Table/Fig-2].

The mean HbA1c, FPG and PPPG values in the different groups have been described vividly in [Table/Fig-3]. Young males documented significantly higher mean values of HbA1c ( $p < 0.05$ ) when compared to males ≥45years, indicating poor metabolic control in the former [Table/Fig-3a].



[Table/Fig-1]: Gender distribution in the study group. (a) Group I: n=212 (45%) (b) Group II: n=260 (55%)

| Variable Parameters    | Mean $\pm$ SD       |                              |                                      |
|------------------------|---------------------|------------------------------|--------------------------------------|
|                        | Study group (n=472) | Group I (<45 years) (n= 212) | Group II ( $\geq$ 45 years) (n= 260) |
| Age (years)            | 49.32 $\pm$ 13.72   | 36.79 $\pm$ 7.2              | 59.63 $\pm$ 8.04                     |
| Duration of DM (years) | 4.82 $\pm$ 3.68     | 4.09 $\pm$ 2.24              | 5.41 $\pm$ 4.45*                     |
| FPG (mg/dl)            | 171.38 $\pm$ 86.08  | 157.2 $\pm$ 79.08            | 183.04 $\pm$ 89.93***                |
| PPPG (mg/dl)           | 268.67 $\pm$ 138.72 | 250.90 $\pm$ 134.36          | 283.29 $\pm$ 140.80**                |
| HbA1c %                | 8.94 $\pm$ 2.77     | 8.70 $\pm$ 2.67              | 9.13 $\pm$ 2.85                      |

**[Table/Fig-2]:** The mean  $\pm$  SD of demographic and clinical variables in the study group.

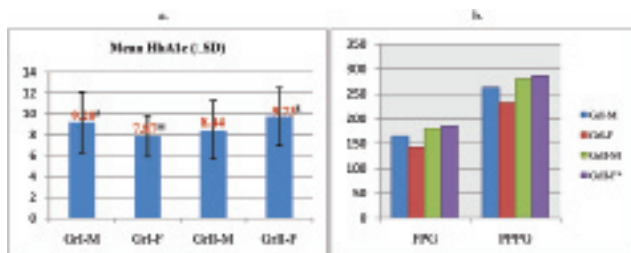
\*p<0.05 \*\*p<0.01 \*\*\*p<0.001

On contrary, the younger females achieve significantly better glycemic control ( $p<0.001$ ) when compared to all other groups [Table/Fig-3a]. The Group II females expressed significantly higher HbA1c, FPG and PPPG levels than their younger counterparts ( $p<0.001$ ) [Table/Fig-3a,3b].

48% of group I males and 35 % of group II males revealed some sort of addiction in the form of alcohol, tobacco, smoking and chewing tobacco and betel nut mixture.

To study any association of duration with glycemic control, the individuals were subdivided as per their duration of diabetes  $\leq$  5 years and  $>$  5 years.

The mean FPG, PPPG and HbA1c values were significantly higher ( $p<0.001$ ) in subjects with duration of diabetes  $>$  5 years [Table/Fig-4].



**[Table/Fig-3]:** Comparison of mean values of HbA1c, FPG & PPPG in the study group.

# p<0.05 (males <45 vs  $\geq$ 45 years)

\*p<0.001 (females <45 vs  $\geq$ 45 years)

@ p<0.001 (males < 45 vs females <45 years)

\$ p<0.001 (females <45 vs  $\geq$ 45 years)

|              | Diabetes duration |             |         |
|--------------|-------------------|-------------|---------|
|              | $\leq$ 5 years    | $>$ 5 years |         |
| FPG (mg/dl)  | 156.34            | 199.63      | p<0.001 |
| PPPG (mg/dl) | 245.8             | 311.63      |         |
| HbA1c %      | 8.23              | 10.27       |         |

**[Table/Fig-4]:** Comparison of FPG, PPPG and HbA1c in the study group categorized as per their duration of diabetes reported in the case file.

To understand the correlation between the variables, Linear regression analysis was performed in the whole study group (n=472), taking HbA1c as the dependent variable and age, duration of diabetes, FPG and PPPG as independent variables. The HbA1c levels correlated linearly with the duration of diabetes ( $p<0.001$ ), FPG ( $p<0.05$ ) and PPPG levels ( $p<0.001$ ) but not with age [Table/Fig-5a].

In order to analyze the contribution of FPG and PPPG towards degree of glycation, we categorized the study population into two groups taking into account their HbA1c level, as per ADA guidelines:

- Subjects with good glycemic control (HbA1c  $<$ 7%)
- Subjects with poor glycemic control (HbA1c  $\geq$ 7%)

In the former, significant linear positive relationship of HbA1c could be established with duration of diabetes ( $p<0.05$ ) and PPPG ( $p<0.01$ ) but not with FPG [Table/Fig-5b]. Whereas, poorly controlled cases, the glycated hemoglobin correlated positively with duration of diabetes ( $p<0.01$ ), FPG ( $p<0.05$ ) and PPPG ( $p<0.05$ ) [Table/Fig-5c].

| (5a)         | Whole study population | p-value   |
|--------------|------------------------|-----------|
| Duration     | 0.1804                 | $<$ 0.001 |
| Age          | -0.0153                | NS*       |
| FPG (mg/dl)  | 0.0055                 | $<$ 0.05  |
| PPPG (mg/dl) | 0.0072                 | $<$ 0.001 |

| (5b)         | HbA1c $<$ 7% | p-value  |
|--------------|--------------|----------|
| Duration     | 0.0631       | $<$ 0.05 |
| Age          | -0.0022      | NS*      |
| FPG (mg/dl)  | 0.0057       | NS*      |
| PPPG (mg/dl) | 0.0045       | $<$ 0.01 |

| (5c)         | HbA1c $\geq$ 7% | p-value  |
|--------------|-----------------|----------|
| Duration     | 0.1005          | $<$ 0.01 |
| Age          | -0.0019         | NS*      |
| FPG (mg/dl)  | 0.0058          | $<$ 0.05 |
| PPPG (mg/dl) | 0.0038          | $<$ 0.05 |

**[Table/Fig-5]:** Relationship between HbA1c values (a) In the whole study population. (b) In the diabetic population with HbA1c  $<$  7%. (c) In the diabetic population with HbA1c  $>$  7%.

\*Note: NS-Non-significant

## DISCUSSION

Recent articles have endorsed the transition of diabetes trend from older to younger generation and the enigma has primarily been attributed to sedentary lifestyle and obesity. Our study deciphered that the percentage of young adults with diabetes (group I; 45%) were at par to their compeer group consisting of adults  $\geq$ 45 years (55%) [Table/Fig-1].

Many researchers also have portrayed similar generation shift imposing it to be an important public health concern for the diabetes care team [17–19].

The number of young females was fewer (37%) [Table/Fig-1a], than other groups and accounted with the lowest HbA1c values [Table/Fig-3a], implying an optimum glycemic control in them over the other subjects. In contrast, more number of females above 45 years (47%) [Table/Fig-1b], fulfilled our inclusive criteria. They exhibited significantly elevated HbA1c, FPG and PPPG ( $p < 0.001$ ) [Table/Fig-3] reflecting poor glycemic control, than their younger counterparts. This could be attributed to the hormonal imbalance during peri and post-menopausal life. Recent studies suggested that ovarian estrogen,  $17\beta$  estradiol, protects human  $\beta$ -pancreatic cell apoptosis induced by pro-inflammatory cytokines in vitro, through activation of estrogen receptor,  $ER\alpha$ . The hormone protects the pancreatic cell death and preserves insulin production, thus mediates its anti-diabetic function [20]. The deficiency of this hormone in peri- and post-menopausal females succumb them to insulin resistance followed by blood glucose upsurge.

Moreover, females in peri and post-menopausal group have higher prevalence of obesity which has been a major risk factor for diabetes [21]. Above all, Indian women are now participating equally with men to run the family. In virtue of workload, they tend to neglect their own health issues and are least concerned about the preventive aspect of diseases. Scavini et al., in their study also estimated significantly higher ( $p < 0.001$ ) prevalence in female Zuni Indians (16.7%) than male Zuni Indians (9.7%). The prevalence of obesity too was significantly higher in female study group (34.3%) compared to the males (21.5%) [22]. Verma et al., also revealed diabetes to be more common in females at slightly higher age group as compared to males [8].

Higher number of male youngsters represented with DM compared to their corresponding female peer group [Table/Fig-1]. Significantly higher HbA1c values in group I males as against group II males ( $p < 0.05$ ) [Table/Fig-3a], predict for a highly compromised metabolic state in young adult males. Family history is one of the major risk factor that lead to early onset DM. Environmental factors also contribute to a major extent like physical inactivity, lack of regular exercise, unhealthy diet habits with lots of junk food and less of fruits and vegetables, altered sleep habits, indulgence in some sort of addiction and lack of sense of responsibility towards their own health. Not only the changing trend in lifestyle but global trend towards urbanization has made the youngsters leave labor-intensive jobs and acquire less strenuous occupations. The above listed risk factors might explain the upturn in diabetic young males lacking desirable glycemic control.

The ICMR-INDIA B study also documented the shift of T2DM to younger age group (25-34 years) in India [4]. Mohan et

al., also described a temporal shift in the age of diagnosis towards the younger group [18]. Ali et al., in their study analyzed poor glycemic control in young adults (19.1%) in comparison to middle-aged adults (15.0%) and elderly subjects (7.3%). They found the same to be more prevalent in young individuals, those who were unmarried, using insulin for treatment and with no insurance coverage [19].

In present study we found that 48% of youngsters were indulged in some sort of addiction like smoking, alcohol and tobacco chewing. Bi Y et al., and Manson et al., had derived that cigarette smoking may be an independent, modifiable risk factor for T2DM [23,24]. They calculated that smoking of 20-25 or more cigarettes a day had a relative risk of diabetes of 1.94 – 2.1. However, moderate alcohol consumption may be associated with reduced risk of diabetes and better insulin sensitivity [25]. Al-Lawati et al., proposed for poor glycemic control in tobacco users [7].

As depicted in [Table/Fig-5a] the linear regression analysis in the whole study population affirmed a significant positive correlation of HbA1c levels with duration of DM ( $p < 0.001$ ). The correlation coefficient value (0.18) implicated that yearly increase in duration would raise the HbA1c level by 0.18%, provided FPG and PPPG remain constant.

Goud et al., presented a significant correlation between glycated hemoglobin and duration of diabetes in their study [21]. Al-Lawati et al., also indicated an inverse relationship of good glycemic control with duration of DM [7]. With advancement of duration of DM, the standard diabetic care may not be actually relevant to them in controlling blood glucose. More intensive lifestyle modification or change in treatment protocol may be required in order to achieve good glycemic index. Many diabetic patients get fed up of taking so many medications, diet restrictions and daily exercises. Young adults also remain resistant to modify their lifestyle. These might account for poor glycemic control with time in present study subjects. Verma et al., also revealed significant rise in HbA1c values with progression in duration of DM. They explained that serum insulin level rises with duration of disease that meant insulin resistance increases with duration of diabetes [8]. Studies have suggested the potential role of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in development of insulin resistance in T2DM. They inhibit the transduction of insulin signaling in glucose metabolism. As a result there is compensatory increase in insulin production by  $\beta$ -pancreatic cells to combat the insulin resistance [26].

The glycated hemoglobin in the study population exhibited significant correlation with FPG ( $p < 0.05$ ) and PPPG ( $< 0.001$ ) that reflected both fasting and postprandial glucose bestowed considerably towards glycation. The HbA1c values rises by 0.55% and 0.72% per 100 mg% increase in FPG and PPPG respectively [Table/Fig-5a]. Cases with HbA1c  $< 7\%$  conferred significant correlation of glycated hemoglobin



with PPPG ( $p < 0.01$ ) but not with FPG [Table/Fig-5b]. This affirms the contribution of post-prandial glucose towards glycosylation of hemoglobin in well controlled individuals. In poorly controlled diabetic individuals, HbA1c correlated with both FPG and PPPG ( $p < 0.05$ ) [Table/Fig-5c]. This signifies that both influence equally towards glycosylation of hemoglobin in uncontrolled diabetics.

The above findings implicate that though PPPG acts as a major contributor for glycosylation of hemoglobin in diabetics as it documented significant positive correlation with HbA1c in all the groups, however PPPG estimation cannot delineate between controlled and uncontrolled glycemia.

Other disadvantages of PPPG analysis is that, its values are highly influenced by various factors like -

- Type of carbohydrate taken – low glycemic index food or high glycemic index food was taken in meal.
- The amount of carbohydrate taken – about 130 g/day is recommended. Low or high amount of carbohydrate also alter the PPPG values
- The recommended 2 hours post meal collection time is not stringently followed.
- Patient compliance to return to lab again after meal is very poor as we found during screening of lab data for FPG and PPPG in the same setting.

Considering the above disadvantages regarding PPPG, FPG would be a better alternative to assess the glycemic index in diabetes. In early identification of changeover of a diabetic from good to poor glycemic control, serial measurements of FPG may be more relevant than PPPG. Further studies may be designed to validate our proposed interpretations.

Haddadinezhad et al., depicted closer association of HbA1c with PPPG rather than FPG and suggested PPPG evaluation should be the focus for assessing metabolic status [5]. Monnier et al., revealed that PPPG contribution was about 70% in good controlled diabetic individuals (HbA1c  $< 7.3\%$ ). This contribution decreased to 30% with worsening of glycemic control (HbA1c  $> 10.2\%$ ) [27]. Contradictory to it, Monami et al., in their study had concluded that fasting glucose provide greater contribution to glycosylated hemoglobin in patients with lower HbA1c [28]. In agreement to Monnier et al., study, another study by Riddle et al., derived that when HbA1c levels rises ( $> 7\%$ ) basal hyperglycemia (BHG) dominates its contribution towards glycosylated hemoglobin. After intensive treatment with basal insulin, the HbA1c level lowers down to the target of 7.0% and contribution shifts to PPPG and that of BHG reduce to one-third only [29]. Ketema and Kibret, indicated that PPPG values correlated strongly with HbA1c and glycemic control per se. Hence, PPPG levels need to be monitored stringently if HbA1c measurement not feasible, to achieve good metabolic control and prevent diabetes related complications [30].

## LIMITATIONS

Major limitations of the study are that of small sample sized retrospective study based on the laboratory data available in the medical record section. Large scale studies by directly recruiting the diabetic patients and following their plasma glucose level regularly for few years would be more informative to show the variation in glycemic control with that of plasma glucose values.

## CONCLUSION

The FPG and PPPG cannot be used as a surrogate indicator of HbA1c status. In order to arrive at any substantial conclusion, large scale properly designed studies needs to be conducted. Our study illustrated significant positive correlation between both FPG ( $p < 0.05$ ) and PPPG ( $p < 0.001$ ) with HbA1c. Though, both FPG and PPPG are contributors for glycation, but PPPG values does not reflect the switch over of glycemic control in diabetics. We hence predict that FPG evaluation might be more beneficial than PPPG in routine monitoring to identify the early flux from good to poor metabolic state in the absence of HbA1c set-up.

Very limited data are available supporting the analysis of sensitivity of FPG and PPPG values to mark out the metabolic status of the patient. However, in our view of point, we think it is of immense public health importance particularly in areas those are deprived of sophisticated infrastructure for laboratory estimation and lack awareness and understanding of the disease which lead to a very poor patient compliance for investigation. Sequential evaluation of FPG of diabetic patients, in absence of HbA1c set up, would definitely aid in developing a feasible strategy for timely diagnoses of diabetics at an early stage of aggravating metabolic derangements and to ensure appropriate management. Large scale population studies would certainly annex to our proposal for a congruous effort towards diabetes management.

## AUTHOR'S CONTRIBUTION

Dr. Suprava Patel contributed towards planning of study design, data analysis, preparing tables and figure, data interpretation and writing the manuscript. Dr. Rachita Nanda immensely supported in planning study design, literature search, data interpretation and writing the article. Dr. Sibasish Sahoo helped in literature search, data collection and data analysis. Dr. Eli Mohapatra contributed towards study design, data interpretation and writing.

## ABBREVIATIONS

HbA1c – Glycosylated hemoglobin A1c  
 FPG – Fasting Plasma Glucose  
 PPPG – Post Prandial Plasma Glucose  
 DM – Diabetes Mellitus  
 WHO - World Health Organization

ICMR – Indian Council of Medical Research

T2DM – Type 2 Diabetes Mellitus

AGE – Advanced Glycation End Product

PKC – Protein Kinase C

ROS – Reactive Oxygen Species

DCCT – Diabetes Control and Complication Trial

ADA – American Diabetes Association

G6PD – Glucose 6-Phosphate Dehydrogenase

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