Disparity Between Plasma Glucose and HbA1c in Assessment of Glycemic Control Among Type 2 Diabetes Patients on Oral Antidiabetic Drugs: A Real-world, Retrospective Study Based on Electronic Medical Records

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Abstract

Background: Disparity between plasma glucose [FPG &PPG] and HbA1c has its implication in diagnosis as well as assessing glycemic control in diabetes. The effect of this disparity in assessing glycemic control during diabetes needs more research.

Objective: Assessment of degree of disparity between fasting, postprandial glucose with HbA1C among type 2 diabetes patients on oral anti-diabetic drugs.

Methodology: A total 12829 electronic medical records [EMR] of people living with diabetes, who attended clinics between Oct-2014 to Jul-2019 were included for the analysis and this data was retrieved from more than 75 physicians across 26 cities. Based on the disparity between plasma glucose and HbA1c, EMRs were categorized in five different categories: Disparity groups [Group A and B], Non-disparity groups [Groups C and D], and Others [Group E].

Results: A disparity of 17.89% [2296] was reported in the study. Mean age and BMI were found to be significantly different among all the five groups. Amongst all the groups, the average duration of diabetes was highest in group D [8.06 years], and there was a significant difference among the five groups. The Pearson correlation coefficient [r] between HbA1c and FPG was found to be 0.71 [P<0.001, 95 % CI; 0.69-0.72] while between HbA1c and PPG it was 0.67 [P<0.001, 95 % CI; 0.66-0.68]. A total of 56 [0.43 %], hypoglycemia episodes were reported based on FPG values, while 108 [0.84 %] were recorded by the physician based on patient's complaints or medical history.

Conclusion: Our study showed disparity between plasma glucose and HbA1c in assessing glycemic control among people living with type 2 diabetes and taking OADs. This disparity should be considered during the management of diabetes.

Keywords: Real-world data, Disparity, Glycemic values, HbA1C value, Oral Anti-diabetic Drugs

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Introduction

Diabetes is a chronic condition associated with multiple microvascular and macrovascular complications in those with poor glycemic control, hypertension, and dyslipidemia [1,2]. Various randomized, prospective clinical trials in type 1 and 2 diabetes have demonstrated that achieving glycemic control significantly decreases the microvascular complications of diabetes. Moreover, each 1% reduction in HbA1c value led to a 37% decrement in the risk of microvascular complications and a further 21% decrease in morbidity and mortality related to diabetes [3,4].

The ADVANCE and UKPDS trials suggest that controlling plasma glucose reduces the development and progression of complications and improves quality-of-life of people living with diabetes [5, 6]. The traditional laboratory tests for diagnosis and clinical monitoring of diabetes patients are fasting plasma glucose [FPG], postprandial plasma glucose [PPG] and glycated hemoglobin [HbA1c] [7]. The limitations for the FPG test include a 12 to 15% day-to-day variation in fasting plasma glucose values, and a slightly lower sensitivity for predicting microvascular complications than HbA1c [8, 9, 10].

HbA1c measurement has been endorsed by the American Diabetes Association [ADA] as a diagnostic and screening tool for diabetes [11]. It is correlated with a range of mean plasma glucose values at a certain value. HbA1c of 6.0% corresponds to mean plasma glucose of 100-152 mg/dl [95% CI] while HbA1c of 7.0% refers to 123– 185 mg/dl [95% CI]. Since there has been overlapping of a single HbA1c value which corresponds to mean plasma glucose ranging from 124 mg/dl to 152 mg /dl, which may lead to inaccurate prediction of mean glucose values [12]. Also, the presence of medical condition such as the hemoglobin variants, malignancies, hemolytic anemia, as well as various medications and pregnancy are factors associated with alterations in the HbA1c values. It may provide unreliable information [13,14]. Not just HbA1c, conventional methods are also of limited help in deciding insulin dose to various situations such as exercise, a meal etc. and understanding day to day variation and intraday variation in plasma glucose values.

The strength of correlation varies within these parameters; Studies showed that there is disparity between PPG and HbA1C and at also the same statement stands real for FPG and HbA1c [3,15]. According to a study conducted on 3523 individuals in Vietnam, the prevalence of diabetes and prediabetes by HbA1c test was estimated to be 9.7% and 34.6%, respectively, while based on the FPG test, the prevalence of diabetes and prediabetes was found to be 6.3% and 12.1%, respectively. Whereas, among 427 individuals diagnosed by FPG as "prediabetes", 28.6% were classified as diabetic by HbA1c test. These findings suggest that there is a significant disparity between FPG and HbA1c in the diagnosis of diabetes. This study concludes that FPG appears to underestimate the burden of undiagnosed diabetes [16]. A cross-sectional survey in the Indian population [N=500] to determine the prevalence of diabetes and prediabetes observed 11.42% and 88.57% were diagnosed as diabetic and prediabetic respectively based on HbA1c. While based on FPG and PPG, 12.85% and 40% were classified as diabetic and prediabetic respectively [17].

On the other hand, epidemiological studies carried out in the general population showed that HbA1c and plasma glucose [FPG and/or PPG] identify partially different groups of people with diabetes. Research study highlighted that Hb1Ac underestimates the burden of undiagnosed diabetes [18, 19]. Similarly, another study conducted in India also highlighted the presence of disparity between the predictive abilities of these three diagnostic tests in diagnosis of diabetes [20]. HbA1c is a good predictor of diabetic complications but has limitations in assessing glycemic variability, hypoglycemia and hyperglycemic excursions. Similarly, plasma glucose [FPG and PPG] do not reflect overall glycemic control and do not provide adequate information about glycemic variability.

The current study has been designed to understand the discrepancy of fasting and postprandial plasma glucose with HbA1c in real-world clinical settings in India among people living with type 2 diabetes and on orally administered antidiabetic drugs [OADs].

Objectives

The present study was done with the following objectives:

[i] To assess the degree of disparity between FPG and PPG with HbA1c among people living with type 2 diabetes and on OADs

[ii] To estimate the correlation of FPG and PPG with HbA1c

[iii] To understand the pattern of hypoglycemia based on conventional glycemic monitoring methods.

Methodology

The electronic medical records [EMR] from multiple diabetes specialty clinics [including more than 75

physicians from 26 cities across India] were systematically evaluated. Anonymized and de-identified data was used for the analysis. EMRs included in the study were of patients, visited the diabetes clinics between October 2014 to July 2019.

Study type: Observational, multicentric, retrospective real-world study

Study settings: The outpatient setting of multiple diabetes clinics across India

Source of data: EMRs of people living with type 2 diabetes

Inclusion Criteria:

[i] Patient with Type 2 diabetes mellitus and managed on OADs

[ii] All records where HbA1c was tested along with FPG or PPG or all were done on the same day or within a period of 15 days of each other.

Exclusion Criteria:

[i] Patients with type 1 diabetes

[ii] Patients on insulin

Statistical analysis:

Patients were categorized into five groups based on HbA1c, FPG, and PPG parameters. Continuous variables are presented as means and categorical variables as proportions. Mean values were compared by using t statistics and Analysis of Variance [ANOVA]. Categorical variables were compared by chi-square statistics. Pearson correlation coefficient was estimated to assess the linear relationship of HbA1c with FPG and PPG.

Definition of five groups:

Patients were classified into five groups based on HbA1c, FPG, and PPG

Disparity Groups

- Group A – HbA1c in range; FPG or PPG out of range [21]
- Group B - HbA1c above range; FPG and PPG in range

Non-disparity Groups

- Group C - All three parameters: HbA1c, FPG, and PPG in range
- Group D - All three parameters: HbA1c, FPG, and PPG out of range

Other Group

- Group E - HbA1c between 7-7.5%

Ethical consideration: Confidentiality of subjects has been maintained by de-identifying personal information and only anonymized data from electronic medical records was used for the analysis.

Results

A total of 12829 patients' electronic medical records were retrieved for analysis. The data were reviewed for all three parameters, namely HbA1c, FPG and PPG, in addition to clinical notes.

Mean age and BMI were found to be significantly different among the five groups. Amongst all groups, the average duration of diabetes was highest in group D [8.06 years], and there was a significant difference among the five groups represented in [Table 1].

Assessment of degree of disparity between FPG and PPG with HbA1c among type 2 diabetes patients on OADs

A total of 2296 patient records [17.89%] showed disparity between plasma glucose and HbA1c [group A & group B]. Whereas 8681 records [67.67%] had an agreement [no disparity] between plasma glucose and HbA1c [group C, and D]. Out of 5986 records [Group D: all three parameters out of range], three [0.05%] patient records had HbA1c > 7.5 and PPBS > 180 and FBS < 70. Only 21.01% of the patient records demonstrated all three parameters in the normal range [group C]. There were 8282 [64.55%] records of patients with at least one of the glycemic variables [Either HbA1c, FPG,

Table 1: Demographic details of the patients.

Group Details	Overall sample N=12829	Mean age [Yrs.]	Male N [%]	Female N [%]	Mean BMI	Mean duration of Diabetes [Yrs.]
Group A	N=1585 [12.35%]	54.65	1074 [67.76]	488 [30.78]	26.24	6.62
Group B	N=711 [5.54%]	55.12	481 [67.65]	216 [30.37]	27.09	7.96
Group C	N=2695 [21.01%]	51.37	1624 [60.25]	1026 [38.07]	27.44	5.35
Group D	N = 5986 [46.66%]	52.7	3985 [66.57]	1926 [32.17]	26.87	8.06
Group E	N = 1852 [14.44]	55.02	1223 [66.03]	599 [32.34]	27.2	8.01
Statistical significance	P < 0.05	P>0.05	P>0.05		P < 0.05	P< 0.05

Table 2: Disparity details among the groups

Name of Group		Group Details	Overall sample N=12829	Disparity [n, %]
Disparity Groups	Group A	HbA1c in range; FPG or PPG out of range	N=1585 [12.35%]	n= 2296 [17.89 %]
	Group B	HbA1c above range; FPG and PPG in range	N=711 [5.54%]	
Non-disparity groups	Group C	All three parameters: HbA1c, FPG, and PPG in range	N=2695 [21.01%]	n= 8681 [66.77 %]
	Group D	All three parameters: HbA1c, FPG, and PPG out of range	N = 5986 [46.66%]	
Other Group	Group E	HbA1c between 7-7.5%	N = 1852 [14.44 %]	n= 1852 [14.44 %]

or PPG] out of range [group A+B+D]. A small group of patients [group B, 5.54%] had normal plasma glucose values, but HbA1c>7.5% [Table 2].

Estimation of the correlation of FPG and PPG with HbA1c

Our study estimated the Pearson correlation coefficient [r] between FPG and HbA1c as 0.71 95 % CI; 0.69-0.72] whereas between HbA1c and PPG was 0.67 [95 % CI; 0.66-0.68] [P<0.001] [Fig 1].

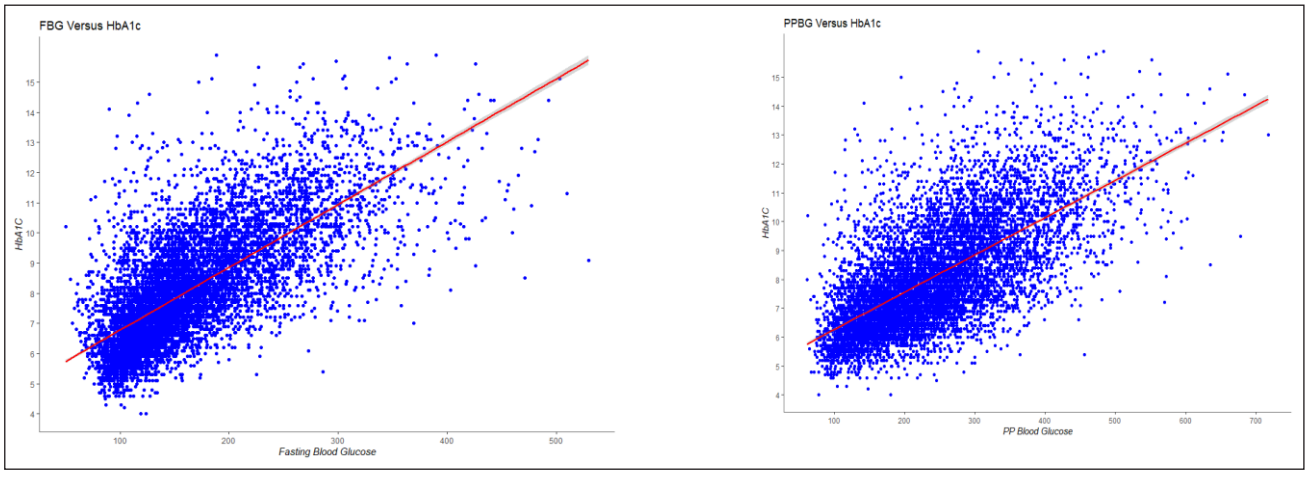
Evaluation of hypoglycemic events based on conventional glycemic monitoring methods and medical history

Hypoglycemic episodes were estimated in two ways 1] if the physician has made the diagnosis of hypoglycemia and recorded it based on patient's complaints or medical history 2] if FPG was found to be <70 mg/dl based on laboratory records.

One hundred eight [0.84%] cases of hypoglycemia were recorded by the physician based on medical history or patient's complaints. Whereas, 56 [0.43%] records were found to be hypoglycemic based on laboratory data [FPG<70 mg/dl]. Five patients had hypoglycemia according to both laboratory reports and physician records. The mean value of HbA1c, PPG and FPG of patients with hypoglycemic [FPG<70] was found to be 6.88 [1.07*], 130.39 [65.69] and 66.45 [9.12] while it was 7.51 [1.62], 184.56 [79.55], and 132.82 [42.33] respectively for the patients, where hypoglycemia was recorded by the physician based on complaints and medical history. The same is presented in [Table 3]. * Standard deviation

Table 3: Mean glycemic values [FPG, PPG, and HbA1c] of patients with hypoglycemia

Variable	Hypoglycemia [based on medical history] recorded by the physician	Lab-based hypoglycemia [FPG <70 mg/dl]
Total N [%] =12829	108 [0.84%]	56 [0.43%]
Mean FPG [SD]	132.82[42.23]	66.45 [9.12]
Mean PPG [SD]	184.56 [79.55]	130.39 [65.69]
Mean HbA1c [SD]	7.51 [1.62]	6.88 [1.07]
Mean age [Yrs.]	58.37	59.04



(a) FPG versus HbA1c **[b] PPG versus HbA1c**

Figure 1. Correlation between HbA1c and [a] FPG [b] PPG

Discussion

Degree of disparity among FPG, PPG, and HbA1c among type 2 diabetes patients on OADs

Our study reported 2296 records of patients [17.89%] having disparity when assessed, including all the three parameters. Moreover, in 5986 patient records [46.66%] all three parameters were out of target range [HbA1c > 7.5%, FPG < 70 or >130 mg/dl, and/or PPG >180 mg/dl]. A total of 8282 patient [64.55%] [Group A+B+D] records had at least one of the three variables out of range. A study by Wolfgang Rathmann et al. [Sample size ~64k T2DM patients] estimated discordance between FPG and HbA1c as 23.38% and 50.70% have at least one glycemic variable out of range [22].

Another study diagnosed type 2 diabetes using the ADA based guidelines and found 12.87% as diabetic by using FPG as criteria, 12.07% using PPG criterion and 14.55% using HbA1c, while 10.51% using FPG, PPG and HbA1c together in combination. Significant discordance [3.28%] was observed between the HbA1c and glucose-based diagnostic criteria for the diagnosis of type 2 diabetes and pre-diabetes in this study [23].

This discrepancy sometime can cause a diagnostic dilemma as well as it makes decision making difficult for diabetes management. These conventional methods are also not adequate to assess patterns and extent of glycemic variability. Glycemic variability [GV] is defined as the oscillation between blood glucose levels within the day and between days, including hypoglycemic events and hyperglycemic peaks. Various research studies have established abnormal variations in glycemic variability as a good predictor for micro and macro-vascular complications of diabetes [24]. And while, glycemic variability is inevitable, it is the abnormal patterns of this that leads to diabetic complications like retinopathy, peripheral neuropathy, urinary albumin excretion, cardiovascular events, and overall mortality [25] and thus management decisions should be taken while keeping GV in consideration.

However, glycemic variability cannot be measured by any of these conventional methods as it requires continuous monitoring of blood glucose to pick up the peaks [hyperglycemic excursions] and troughs [hypoglycemic events] that occur throughout the day. HbA1c reflects average glucose levels, but not variability; hence the measurement of GV required other methods of analysis [26]. In an International consensus on the use of CGM inferred HbA1c values do not reflect inter day and intraday glycemic excursions [27].

Correlation of FPG and PPG with HbA1c

The present study reported a significant difference [p<0.001] in the Pearson correlation coefficients [r] between FPG and HbA1c [0.71 {95% CI; 0.69-0.72}] and PPG and HbA1c [0.67 {95% CI; 0.66-0.68}]. Another study reported the Pearson correlation coefficient [r] between FPG and HbA1c and PPG and HbA1c as 0.62 and 0.22, respectively [28]. Similar findings are published in a study, the Pearson correlation coefficient between FPG and HbA1c was 0.551, and between PPG and HbA1c was 0.475 [29]. The same trends in the correlation between FPG, PPG and HbA1c have also been reported by other studies as well [30, 31]. This highlights that while a significant linear correlation exists between the values of FPG and PPG with Hb1c, and both are good predictor of HbA1c, though it is 100% linear relationship [r=1] and other factors also must play a role in determination of HbA1c concentration such as RBC life span, anemia, etc.

Burden of hypoglycemia in Type 2 DM

Our study reported a total of 164 [1.2%] hypoglycemic events. A nested case-control analysis in the UK reported 4% hypoglycemia in T2DM patients [sample 50048] taking OADs [32]. This study identified hypoglycemia event from records and classified them into mild/ moderate and severe based on their management by GP or in emergency respectively. It is difficult to compare rates of hypoglycemia incidence as different studies use different monitoring approaches and diagnostic criteria.

Another study reported that the prevalence of hypoglycemic events as 16% [56/346] among patients on OADs alone. In this study patients monitored their glucose levels when experiencing symptoms using home-based blood glucose monitoring [33].

The limitations of conventional diagnostic methods have paved the way for continuous glucose monitoring [CGM]. The CGM provides patients with real-time information about glucose levels, rate of change, and glucose trends [34]. The use of CGM has been documented to decrease plasma glucose excursions, lower HbA1c values, and reduce hypoglycemic episodes, which together diminish the risk of complications associated with diabetes [35]. Many clinical studies concluded a reduction in HbA1c in the CGM group compared with the other group [36-38]. Recently, a consensus was released in 2019 on the use of Ambulatory Glucose Profile [AGP] in Indian T2DM patients on OADs. The recommendations were made for the usage of AGP in T2DM patients on OADs where there is a disparity between FPG/PPG levels and HbA1c [HbA1c>7.5% with

FPG/PPG levels on target or HbA1c on target with FPG/PPG levels not on target], in patients at risk/with hypoglycemic episodes, or for patients who are not adherent to lifestyle modification or are noncompliant to treatment [39]. A consensus on CGM released in 2019 summarised CGM as a reliable tool for monitoring GV and achieving glycaemic targets both in T1DM and T2DM [40]. Thus, CGM can enable patients to become more aware of these silent changes in plasma glucose values, provide them with an opportunity to understand their glycemic status and make the necessary adjustments in lifestyle to avoid these hypoglycemic episodes potentially.

Study strengths and limitations

Though various studies highlighted discordance between plasma glucose [FPG & PPG] and HbA1c in the diagnosis of diabetes. This is one of the few real-world studies which have estimated discordance between HbA1c and plasma glucose values in assessing glycemic control in the course of diabetes. It also highlights the discrepancy in a special section of diabetes patients, who are taking only oral antidiabetic medications. This study is an effort to induce a thought process among healthcare providers regarding the limitations of conventional methods in assessing glycemic control.

Conclusion

Conventional methods are not adequate in estimating the incidence and burden of hypoglycemic events and hyperglycemic excursions, which get reflected by the very low rate of hypoglycemic events reported in the study. Though to measure the incidence of symptomatic hypoglycemia, more meticulous studies are required [based on SMBG or CGM]. Disparity between plasma glucose and HbA1c is significant and has the potential to affect patient care if clinical decision is purely based on these methods. Our study concludes that physicians should take into consideration all the three variables [HbA1c, FPG, and PPG] and the existing disparity before concluding for the management of diabetic patients.

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