Correlation between Estimated Average Glucose Levels Calculated from HbA1c Values and Random Blood Glucose Levels in a Cohort of Subjects

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Abstract

Objective Hemoglobin A1c (HbA1c) level remains the gold standard test for the assessment of glycemic control, and it reflects the mean glucose values in the previous 3-month period. HbA1c is expressed as a percentage, whereas the monitoring and treatment of diabetes are based on blood glucose levels expressed as mg/dL. It is appropriate to make it easy for the patient to understand both random blood sugar (RBS) and estimated average glucose (eAG) expressed with the same units. This will enhance the usefulness of eAG. This article determines the statistical correlation between eAG derived from HBA1C with RBS values both in diabetic and prediabetic subjects.

Methods The RBS and HbA1c levels of 178 males and 283 females (12–90 years) were obtained and the eAG levels were calculated using Nathan's regression equation. The samples were divided into four groups based on HbA1c levels—group 1: HbA1c greater than 9%, group 2: HbA1c 6.5 to 9%, group 3: HbA1c 5.7 to 6.4%; and group 4: HbA1c less than 5.7%.

Results There was a statistically significant positive correlation between RBS and eAG values for the study group 1 and 2. Also, the median values of RBS and eAG showed a significant difference ($p < 0.001$).

Keywords
► HbA1c
► glycated hemoglobin
► eAG
► estimated average blood glucose

Conclusion As the association between the RBS and eAG levels is strong in a fairly and poorly controlled diabetic population, reporting the eAG level together with the HbA1c level at no additional cost may assist in effective blood glucose control in clinical care. However, eAG and RBS values cannot be used interchangeably.

Introduction

The prevalence of diabetes mellitus (DM) in India has risen from 7.1% in 2009 to 8.9% in 2019. Currently, 25.2 million adults are estimated to have impaired glucose tolerance, which is estimated to increase to 35.7 million in the year 2045. India ranks second after China in the global diabetes

epidemic with 77 million people with diabetes.[1] In Delhi, capital of India, 25.2% of the population was estimated to have diabetes.[2] Among the various biochemical markers associated with DM diagnosis and management, glycated hemoglobin A1c (HbA1c) is of utmost importance owing to its utility as a reliable marker to assess timely control over the preceding 2 to 3 months.[3] It is recommended that diabetic patients have their HbA1c levels checked at least two times per year because quantitative and direct relationships have been identified between HbA1c concentration and the risk of diabetic microvascular complications.[4] Therefore, clinicians use HbA1c test results to guide treatment decisions, and the test has become the cornerstone for assessing diabetes care.[5] The conventional approach for the expression of HbA1c values is percent (%) of total hemoglobin, which is not easily comprehensible for a DM patient with nonmedical background.[6]

In 2008, Nathan et al conducted the International HbA1c-Derived Average Glucose (ADAG) trial, which established a linear dependence between HbA1c and averaged plasma glucose levels, and a simple mathematical equation for the calculation of estimated average glucose (eAG) level using the HbA1c level was introduced.[7] The relationship between HbA1C and eAG is described by the equation $28.7 \times A1C - 46.7 = eAG$. This equation has been extensively evaluated since then, and citing eAG values with HbA1c laboratory reports has become a common practice. Still most clinical laboratories have not yet started reporting eAG values and a widespread understanding of its utility in the medical fraternity is missing.

Objectives

1. To determine the statistical correlation between HBA1C with random blood sugar (RBS) values both in diabetic and prediabetic subjects.
2. To determine the statistical correlation between eAG derived from HbA1C using the Nathan's regression equation with RBS both in diabetic and prediabetic subjects.
3. To analyze the significance of eAG as opposed to HbA1C as a marker of long-term glycemic control in DM.

Materials and Methods

Study Design
This hospital-based retrospective analytical cohort study was conducted at the Clinical Laboratory, Department of Biochemistry, Hindu Rao Hospital (900-bedded tertiary care hospital), New Delhi, India after approval from the institutional ethical review committee (IEC/NDMC/2022/131).

Sample Selection and Sample Size
The study group was selected from patient reporting to the laboratory for HbA1c estimation. The simple random sampling technique was used to obtain laboratory records of both sexes in the age range of 12 to 90 years presenting as outpatients. Pregnant females and patients diagnosed with renal disorder were excluded from the study. For an

estimated prevalence of 25.2% of diabetes in Delhi population[2] and with 5% absolute precision, 95% confidence interval, and 10% confounding variable, we needed a sample size of 320.

Data Collection
The random blood glucose and HbA1c levels of 461 patient samples (178 male and 283 female) were included in the study. Blood samples were taken on the same day for the determination of both RBS and HbA1c. The eAG levels (mg/dL) were calculated using the following formula: $28.7 \times HbA1c - 46.7$. The samples were divided into four groups on the basis of HbA1c levels as group 1: HbA1c greater than 9% (poorly controlled diabetic), group 2: HbA1c 6.5 to 9% (fairly controlled diabetic), group 3: HbA1c 5.7 to 6.4% (prediabetic), and group 4: HbA1c less than 5.7% (nondiabetic).[8]

Glucose levels were determined using the glucose oxidase method in Transasia Erba analyzer with commercially available Agappe kits. HbA1c levels were determined using high-performance liquid chromatographic method on Biorad D10 analyzer with Biorad kits.

Statistical Analysis

Presentation of categorical variables was done in the form of number and percentage (%). Quantitative data were presented as the means ± standard deviation (SD) and as median with 25th and 75th percentiles (interquartile range). Data normality was checked by using the Kolmogorov–Smirnov test. The cases in which the data was not normally distributed, we used nonparametric tests. The following statistical tests were applied for the results:

1. The association of the variables which were quantitative and not normally distributed in nature was analyzed using Mann–Whitney *U* test (for two groups) and Kruskal–Wallis test (for more than two groups). Wilcoxon signed ranks test was used for comparison of RBS (mg/dL) and eAG (mg/dL).
2. Spearman's rank correlation coefficient was used for correlation of RBS (mg/dL) with HbA1c (%) and RBS (mg/dL) with eAG (mg/dL).

Data entry was done in Microsoft Excel spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software (ver 21.0, IBM, Chicago, Illinois, United States). A *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 461 patients' data (178 males, 283 females) were recorded for the study. Age range was between 12 and 90 years and mean age ± SD was 46.89 ± 13.2 years. The mean ± SD values of HbA1c, eAG, and RBS of the total population were $7.8 \pm 2.54\%$, 177.2 ± 72.89 mg/dL, and 169.53 ± 86.1 mg/dL, respectively (►**Table 1**, ►**Fig. 1A** and **B**). There was a statistically significant difference found in all the dependent variables (HbA1c/RBS/eAG) in two independent groups, that is, males

Table 1 Distribution of baseline characteristics of study subjects

Baseline characteristics	Frequency	Percentage
Gender		
Female	283	61.39
Male	178	38.61
HbA1c (%)		
> 9% (poorly controlled diabetic)	131	28.42
6.5–9% (fairly controlled diabetic)	152	32.97
5.7–6.4% (prediabetic)	79	17.14
< 5.7% (nondiabetic)	99	21.48
Mean ± SD	7.8 ± 2.54	
Median (25th–75th percentile)	7 (5.8–9.5)	
Range	4–16.6	
Age (y)		
Mean ± SD	46.89 ± 13.2	
Median (25th–75th percentile)	47 (38–57)	
Range	12–90	
Random blood sugar (mg/dL)		
Mean ± SD	169.53 ± 86.1	
Median (25th–75th percentile)	139 (108–204)	
Range	61–627	
Estimated average glucose (mg/dL)		
Mean ± SD	177.2 ± 72.89	
Median (25th–75th percentile)	154.2 (119.76–225.95)	
Range	68.1–429.72	

Abbreviations: HbA1c, hemoglobin A1c; SD, standard deviation.

and females (►**Table 2**). It showed males have significant higher values of HbA1c, RBS, and eAG as compared with females (►**Fig. 2**). The study sample was divided into four groups on the basis of HbA1c values (group 1 HbA1c > 9%, group 2 HbA1c 6.5–9%, group 3 HbA1c 5.7–6.4%, and group 4 < 5.7%). A nonparametric test applied to the four groups showed a statistically significant difference in their RBS and

eAG values (►**Table 3**, ►**Fig. 3**). As shown in ►**Table 4** (►**Fig. 4A** and **B**) there was a statistically significant positive correlation in both cases: RBS versus HbA1c and RBS versus eAG ($r = 0.782$, $p \leq 0.0001$, $R^2 = 0.612$) for the whole study sample. We also observed similar positive correlation in group 1 sample ($r = 0.447$, $p \leq 0.0001$, $R^2 = 0.1998$) and group 2 sample ($r = 0.322$, $p \leq 0.0001$, $R^2 = 0.1037$). No statistically significant relationship was observed between RBS and eAG in group 3 ($r = 0.111$, $p > 0.05$) and group 4 ($r = 0.082$, $p > 0.05$).

►**Table 5** (►**Fig. 5**) depicts these median values of RBS and eAG show statistically significant difference ($p < 0.001$).

Discussion

One limitation often associated with HbA1c is the reporting units of mmol/mol and %, which differs from the usual units of blood glucose monitoring, that is, mg/dL, often creating a confusing situation for the patients as well as clinicians for comprehension.[10]

To overcome these limitations, international bodies including the American Diabetes Association and the International Diabetes Federation proposed a mathematical expression termed eAG, which facilitates comprehension of HbA1c values in units parallel to self-monitoring.[11] Various guidelines recommend reporting eAG with every HbA1c report; however, it is not widely practiced by the majority of laboratories, and advocacy is required regarding its use based on evaluation in the local population.[12] With this perspective in mind, we planned to study the association between RBS and eAG in a cohort of subjects.

This is the first study in Indian population correlating eAG values with RBS values in both diabetics and nondiabetic subjects. In this study, we found statistically significant correlation of RBS with eAG in total study subjects and diabetics (poorly controlled and fairly controlled groups) but no significant correlation was found between eAG and RBS in nondiabetic and prediabetic groups, which is similar to Kim et al findings. We also found in our study that RBS values cannot be used interchangeably with eAG values. Most of the below mentioned studies highlighted an association between eAG/HbA1c and RBS/fasting blood sugar
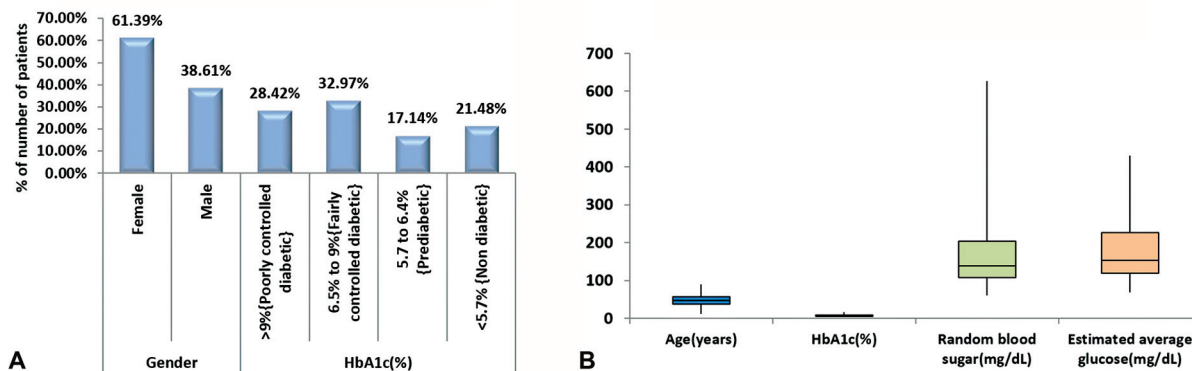

Fig. 1 (A) Distribution of baseline characteristics of study subjects. (B) Descriptive statistics of age (years), hemoglobin A1c (HbA1c) (%), random blood sugar (mg/dL), and estimated average glucose (mg/dL) of study subjects.

Table 2 Association of parameters with gender

Parameters	Female (n = 283)	Male (n = 178)	Total	p-Value
Age (y)				
Mean ± SD	45.41 ± 13.31	49.25 ± 12.68	46.89 ± 13.19	0.004[a]
Median (25th–75th percentile)	45 (35–56)	50 (41–57.75)	47 (38–57)	
Range	18–80	12–90	12–90	
HbA1c (%)				
Mean ± SD	7.53 ± 2.38	8.23 ± 2.73	7.8 ± 2.54	0.008[a]
Median (25th–75th percentile)	6.8 (5.6–8.95)	7.4 (6.1–10.075)	7 (5.8–9.5)	
Range	4.1–14.4	4–16.6	4–16.6	
Random blood sugar (mg/dL)				
Mean ± SD	162.14 ± 81.64	181.27 ± 91.75	169.53 ± 86.1	0.022[a]
Median (25th–75th percentile)	134 (106.5–190)	150 (114.25–228.75)	139 (108–204)	
Range	61–627	71–500	61–627	
Estimated average glucose (mg/dL)				
Mean ± SD	169.42 ± 68.22	189.56 ± 78.38	177.2 ± 72.89	0.008[a]
Median (25th–75th percentile)	148.46 (114.02–210.165)	165.68 (128.37–242.453)	154.2 (119.76–225.95)	
Range	70.97–366.58	68.1–429.72	68.1–429.72	

Abbreviations: HbA1c, hemoglobin A1c; SD, standard deviation.
[a]Mann–Whitney U test.

(FBS)/postprandial blood sugar (PPBS)/self-monitored mean blood glucose (MBG) in diabetics, this association had not been checked in diabetic, prediabetic, and nondiabetic subgroups separately, possibly due to the study design which only included diabetics.

These studies represent association in patients labeled with DM divided into three groups on the basis of FBS/PPBS values as good control, moderate control, and poorly controlled glycemic state subjects, stating the statistically significant correlation of eAG with FBS and PPBS in total diabetic population under study and poorly controlled diabetic subjects. A study by Kariyawasan found a significant statistical

Fig. 2 Association of parameters with gender (nonparametric variables).

correlation in both FBS and PPBS with eAG in the groups of patients with moderately poor control. In those with markedly poor control the FBS did not show a statistical correlation with eAG, as opposed to the PPBS.[9] Bozkaya et al have found that a strong positive correlation exists between fasting plasma glucose (FPG) levels and estimated average blood glucose levels ($r = 0.757$, $p = 0.05$).[10] Rosediani et al revealed that both PPBS and FBS correlated significantly with HbA1c but PPBS showed better correlation with HbA1c than FBS ($r = 0.604$ vs. 0.575).[13] Mahato et al found statistically significant correlation of eAG with FBS ($r = 0.61$, $p < 0.001$) and post prandial (PP) blood sugar levels ($r = 0.65$, $p < 0.001$).[14] Kim et al found that FPG showed a moderate correlation with eAG ($r = 0.672$, $p < 0.001$) in all subjects but when diabetic and nondiabetic subjects were divided into subgroups according to the FPG level, the correlation between eAG and FPG decreased in both subgroups as the FPG level decreased.[15] Guan et al found the relationship between HbA1c and FPG changed according to the different FPG ranges. [16] Azim et al found direct correlation between HbA1c and RBS in diabetics.[17] Ram et al found significant difference in eAG and FBS values.[18] Nkoana and Khine found a positive correlation between self-monitored MBG and HbA1c in all participants ($R^2 = 0.69$, $p < 0.0001$) but clinically significant differences between MBG and eAG values.[19]

There were few limitations of this study. Notably, we did not categorized patients into type 1 and type 2 diabetics. Moreover, as the complete blood picture was not available for all subjects, anemic and other endocrine disorder cases were not excluded.
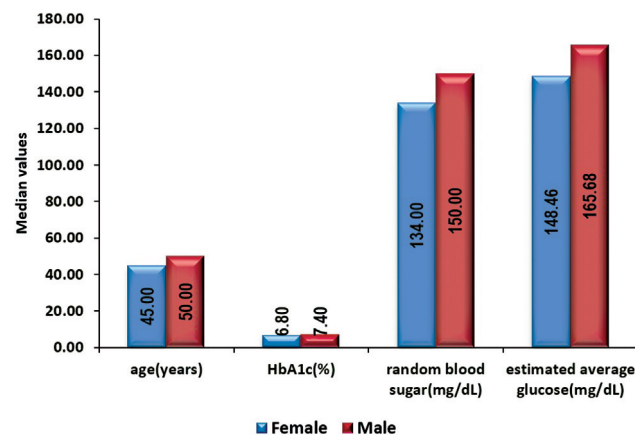
Table 3 Association of parameters with HbA1c (%)

Parameters	> 9% (poorly controlled diabetic) (n = 131)	6.5–9% (fairly controlled diabetic) (n = 152)	5.7–6.4% (prediabetic) (n = 79)	< 5.7% (nondiabetic) (n = 99)	Total	p-Value
Age (y)						
Mean ± SD	49.19 ± 11.52	50.89 ± 11.11	48.09 ± 11.39	36.76 ± 14.52	46.89 ± 13.19	< 0.0001[a]
Median (25th–75th percentile)	50 (40–56.5)	51 (44–60)	50 (40.5–56)	35 (26–42)	47 (38–57)	
Range	18–80	21–85	24–78	12–90	12–90	
HbA1c (%)						
Mean ± SD	11.25 ± 1.6	7.49 ± 0.73	6.06 ± 0.22	5.1 ± 0.38	7.8 ± 2.54	< 0.0001[a]
Median (25th–75th percentile)	10.9 (10–12.1)	7.4 (6.875–8.1)	6.1 (5.9–6.2)	5.2 (4.85–5.4)	7 (5.8–9.5)	
Range	9.1–16.6	6.5–9	5.7–6.4	4–5.6	4–16.6	
Random blood sugar (mg/dL)						
Mean ± SD	258.16 ± 96.56	162.29 ± 51.68	121.54 ± 32.5	101.65 ± 19.37	169.53 ± 86.1	< 0.0001[a]
Median (25th–75th percentile)	243 (197–322)	151.5 (128.75–176.25)	114 (104–127.5)	97 (89–110.5)	139 (108–204)	
Range	82–627	85–385	61–295	69–164	61–627	
Estimated average glucose (mg/dL)						
Mean ± SD	276.23 ± 45.87	168.29 ± 21.04	127.28 ± 6.32	99.67 ± 10.88	177.2 ± 72.89	< 0.0001[a]
Median (25th–75th percentile)	266.13 (240.3–300.57)	165.68 (150.612–185.77)	128.37 (122.63–131.24)	102.54 (92.495–108.28)	154.2 (119.76–225.95)	
Range	214.47–429.72	139.85–211.6	116.89–136.98	68.1–114.02	68.1–429.72	

Abbreviations: HbA1c, hemoglobin A1c; SD, standard deviation.
[a]Kruskal–Wallis test.

Conclusion

In conclusion, in poorly controlled diabetic care-sensitive group, eAG can serve as easily comprehensible way to determine average glucose levels with the same reporting units for self-blood glucose monitoring. This will supplement clinicians to facilitate care and counsel patients in a more convincing way. Moreover, it can serve as a useful measure for clinical laboratories of government hospitals in developing countries to enhance the quality of reporting at no added substantial cost.
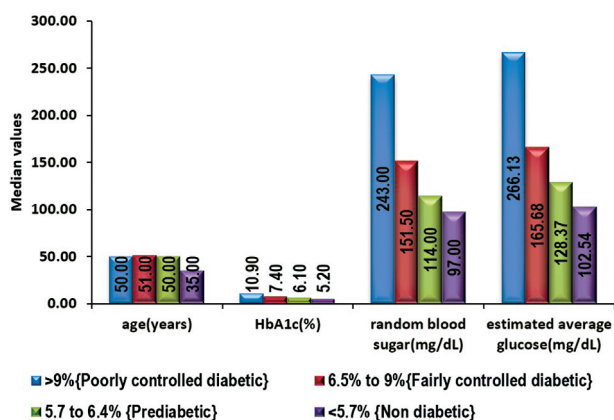

Fig. 3 Association of parameters with hemoglobin A1c (HbA1c) (%) (nonparametric variables).

Table 4 Correlation of random blood sugar (mg/dL) with HbA1c (%) and random blood sugar (mg/dL) with estimated average glucose (mg/dL)

Variables		Random blood sugar (mg/dL) and HbA1c (%)	Random blood sugar (mg/dL) and estimated average glucose (mg/dL)
Total study subjects	r	0.782	0.782
	R^2	0.612	0.612
	p-value	< 0.0001	< 0.0001
Female	r	0.788	0.788
	R^2	0.621	0.621
	p-value	< 0.0001	< 0.0001
Male	r	0.763	0.763
	R^2	0.582	0.582
	p-value	< 0.0001	< 0.0001
> 9% (poorly controlled diabetic)	r	0.447	0.447
	R^2	0.1998	0.1998
	p-value	< 0.0001	< 0.0001
6.5–9% (fairly controlled diabetic)	r	0.322	0.322
	R^2	0.1037	0.1037
	p-value	0.0001	0.0001
5.7–6.4% (prediabetic)	r	0.111	0.111
	R^2	0.0123	0.0123
	p-value	0.328	0.328
< 5.7% (nondiabetic)	r	0.082	0.082
	R^2	0.0067	0.0067
	p-value	0.422	0.422

Abbreviation: HbA1c, hemoglobin A1c.
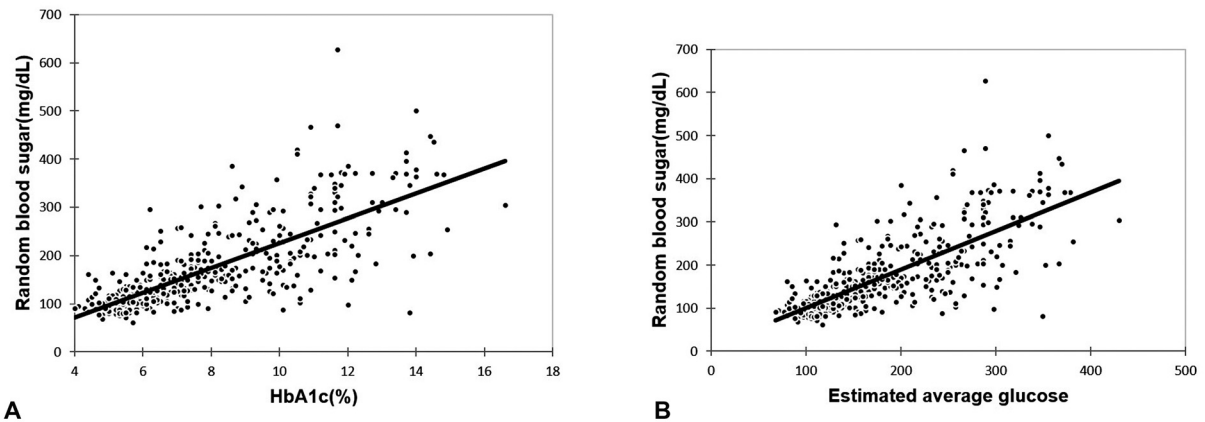Note: Spearman rank correlation coefficient.

Fig. 4 (A) Correlation of hemoglobin A1c (HbA1c) (%) with random blood sugar (mg/dL) in total study subjects. (B) Correlation of estimated average glucose with random blood sugar (mg/dL) in total study subjects.

Table 5 Descriptive statistics of glycemic parameter of study subjects

Glycemic parameter	Mean ± SD	Median (25th–75th percentile)	Range	p-Value
Random blood sugar (mg/dL)	169.53 ± 86.1	139 (108–204)	61–627	< 0.0001[a]
Estimated average glucose (mg/dL)	177.2 ± 72.89	154.2 (119.76–225.95)	68.1–429.72	

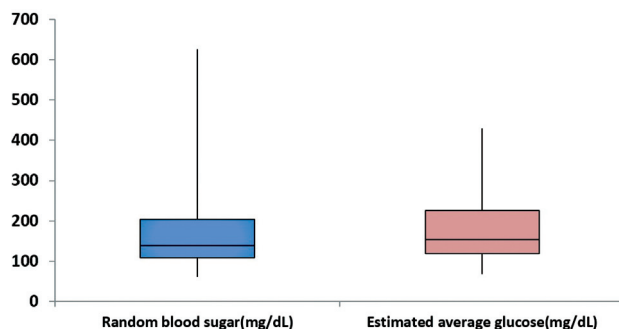Abbreviation: SD, standard deviation.
[a]Wilcoxon signed ranks test.

Fig. 5 Descriptive statistics of random blood sugar (mg/dL) and estimated average glucose (mg/dL) of study subjects.

Conflict of Interest
None declared.

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