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ORIGINAL ARTICLE

Can Fasting Blood Sugar be Used as an Indicator of Long-Term Diabetic Control Instead of Estimated Average Glucose?

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SUMMARY

Background: **Diabetes mellitus is a chronic illness that is a worldwide issue. HbA1c has been used to monitor glycemic control in patients with diabetes for many years. Although HbA1c measurement is needed for calculating estimated average blood glucose (eAG), it is now recommended that eAG is used instead of HbA1c for expression of blood glucose control and communication with patients and health care providers. This study, investigated fasting blood glucose (FBS) as an indicator of overall chronic blood sugar control by assessing the correlation between FBS with eAG derived from HbA1c.**

Methods: **The blood samples for HbA1c assay were collected in EDTA tubes and were analyzed by an HPLC analyzer (G8 Tosoh, Japan). Blood samples for FBS were collected in serum separator tubes, transported, and centrifuged for 15 minutes at 3,000 g. FBS levels were determined in serum samples with the enzymatic hexokinase method by a clinical chemistry analyzer (Architect 8000, Abbott, USA).**

Results: **Statistical analysis was performed on 1,740 patients with type 2 diabetes mellitus with HbA1c levels above 6.5 mmol/L. The difference between FBS (9.3 ± 3.7 mmol/L) and eAG (11.14 ± 2.7 mmol/L) was statistically significant ($p < 0.0001$). The correlation coefficient between FBS and eAG was $r = 0.65$ (95% CI; 0.62 - 0.69), with a p-value < 0.0001.**

While the correlation coefficient between FBS and eAG at HbA1c < 6.5% was $r = 0.251$ (95% CI, 0.16 - 0.34), with a significant p-value of < 0.00001.

The combined data, standard deviation (SD), median, and interquartile range of eAG and FBS for all of the diabetic groups (n = 2,315), were 10.1 ± 3.00 mmol/L, 9.5 mmol/L, and 7.75 - 12.03 mmol/L for eAG, respectively. Similarly, these values were 8.5 ± 3.6 mmol/L, 7.5 mmol/L, and 6.0 - 10.00 mmol/L for FBS, respectively.

Conclusions: **We concluded that there is a moderate and significant positive correlation between fasting blood sugar and the estimated average blood glucose derived from HbA1c. Although FBS might be helpful for daily monitoring of diabetes. Further studies must be conducted to provide solid results to support that FBS and its derived variable eAG can replace HbA1c as an indicator of long-term overall control of T2DM patients.**

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KEY WORDS

glycated haemoglobin, HbA1c, estimated average glucose, eAG, fasting blood sugar, FBS

INTRODUCTION

Diabetes mellitus is a chronic illness that is a major health issue in Saudi Arabia and all over the world [1]. The most recent epidemiological survey that was conducted in Saudi Arabia and included all regions suggested that 23.7% of adults between the ages of 30 - 70 years have diabetes [1]. Similarly, high prevalence rates have been reported from different Arab countries [2]. Worldwide, it is estimated that the prevalence of diabetes will double over the next 20 years [3,4]. It has been shown that tight control of diabetes significantly decreases the risk of microvascular and, most likely, macrovascular complications [5,6]. Monitoring diabetes control depends on the measurement of blood sugar by the patient using portable glucometers (glucose home monitoring) [7]. The diagnosis and follow up of diabetic patients depend on the measurement of fasting and random blood glucose by a central hospital laboratory. In routine clinical practice, more emphasis is placed on the measurement of glycated hemoglobin (HbA1c) every 2 to 3 months because this test has been shown to be reliable in assessing blood sugar control and correlates well with the risk of microvascular complications [8].

HbA1c has been used to monitor glycemic control in patients with diabetes for many years. The critical importance of the test was not fully realized until the Diabetes Control and Complications Trial (DCCT) showed a strong relationship between HbA1c and risk for diabetic complications [5,9,10]. After the DCCT was completed, specific diabetes treatment goals were established; a general goal for most patients with diabetes was an HbA1c of < 7% [8,11,12]. HbA1c is most commonly reported as the percentage of hemoglobin that is glycated. Although this measurement gives a clear indication of blood sugar control over the last 2 to 3 months, the exact relationship between HbA1c and the daily fasting blood sugar levels measured by the patient or by the laboratory is unclear. For example, an HbA1c of 10% is clearly elevated and indicates poor control of diabetes, but to what extent blood sugar was elevated was not clear from the reading of HbA1c. This problem was a complicated issue in the management of diabetes for physicians and confusing for patients, who frequently do not understand the relationship between hemoglobin and blood glucose. Thus, attempts were made to identify a precise relationship between blood glucose measurements and HbA1c [13-15]. In a recently published multicenter study, it was found that HbA1c can be expressed in blood sugar units using an equation that defines the relationship between HbA1c and the average blood sugar over the last 2 to 3 months [14]. Estimated average glucose (eAG) is a new way to determine how well a patient is controlling his/her diabetes [14]. eAG is derived from HbA1c by an equation (eAG = 1.59 x [HbA1c] - 2.59), and the results are presented in mmol/L [14]. Because eAG is not measured and is only derived from HbA1c, it has shortcomings that are similar to those of HbA1c, including the time needed to obtain the result and unavailability in many medical centers, especially peripheral centers.

Although HbA1c measurement is needed for calculating estimated blood glucose (eAG), it is now recommended that eAG is used instead of HbA1c for expression of blood glucose control and communication with patients and health care providers [13-15]. HbA1c, from which eAG is derived is not always available, especially in primary care centers. However, fasting (FBS) and random blood sugar measurements are widely available and easily obtainable in most laboratories and clinics, but it is not clear to what extent these tests are related to eAG derived from HbA1c. If a close correlation is found between randomly obtained FBS with eAG, FBS may serve as a surrogate marker or an alternative to the measurement of HbA1c when it is not available. FBS has been shown to predict long-term complications [16-18]. However, it is generally used as a quick test to evaluate the current blood sugar level. Therefore, our objective in this study is to investigate FBS as an indicator of overall chronic blood sugar control by assessing the correlation between FBS with eAG derived from HbA1c.

MATERIALS AND METHODS

Patients

We randomly reviewed the records of 5,000 patients with T2DM treated with insulin or oral glucose-lowering medication who simultaneously had measurements of HbA1c and FBS levels at the same time or close together from January to December 2009. Among 5,000 patients, only 1,740 patients fulfilled our inclusion criteria, which included serial high FBS levels greater than 7.0 mmol/L on different dates for each patient. Data were extracted retrospectively from our laboratory information system (LIS) using the Cerner Classic system (Cerner, USA). Cases in which there were no simultaneous readings of FBS and HbA1c were excluded. The estimated average glucose (eAG) values were calculated using the following equation: AG (mmol/L) = 1.59 * A1c - 2.59. Based on the study of Nathan et al. [14], the differences between eAG and actual FBS were also calculated. To restrict our study to patients with a definite diagnosis of DM, we included only patients with an HbA1c $\geq$ 6.5% and who also had at least one simultaneous reading of FBS. The normal HbA1c range (< 6.5%) was recommended by the International Diabetes Federation and American College of Endocrinology [19]. Therefore, we also calculated eAG from values of HbA1c below 6.5% to compare with those above 6.5%. We excluded patients who had no simultaneous readings of FBS (not performed within one week of Hb-

A1c). In this study, lab-to-lab variations were eliminated in HbA1c results because all of the samples were analyzed on the same day and in the same laboratory.

Laboratory analysis

The blood samples for HbA1c assay were collected in EDTA tubes and immediately delivered to the central laboratory of King Abdulaziz Medical City in Riyadh, Saudi Arabia. The samples were analyzed for HbA1c level by an HPLC analyzer (G8 Tosoh, Japan). In contrast, blood samples for FBS were collected in serum separator tubes, transported, and centrifuged for 15 minutes at 3,000 g. FBS levels were determined in serum samples with the enzymatic hexokinase method by a clinical chemistry analyzer (Architect 8000, Abbott, USA).

Statistical analysis

Numerical data are presented as the mean ± SD or median and range, and categorical data are presented as numbers and percentages. The difference between FBS and eAG was compared using an independent *t*-test. The p-value was significant at < 0.01. Pearson's correlation tests were used to correlate eAG and HbA1c with FBS.

RESULTS

Table 1 shows the mean, standard deviation (SD), median, and interquartile range of HbA1c, eAG, and FBS. Statistical analysis was performed on 1,740 patients with type 2 diabetes mellitus with HbA1c levels above 6.5 mmol/L. In total, there were 822 (47.2%) male patients and 918 (52.8%) female patients. The mean age of the patients was 57.9 ± 10 years. The median and interquartile range of the patient ages were 56 and 50.9 - 64.2 years, respectively. The mean ± SD, median, and interquartile range of HbA1c were 8.64 ± 1.7%, 8.3% and 7.2 - 9.7%, respectively. The mean ± SD, median, and interquartile range for eAG were 11.14 ± 2.7 mmol/L, 10.6 mmol/L and 8.8 - 12.8 mmol/L, respectively. Similarly, the mean ± SD, the median and interquartile range for FBS were 9.3 ± 3.7 mmol/L, 8.3 mmol/L and 6.8 - 10.97 mmol/L, respectively. The difference between FBS (9.3 ± 3.7 mmol/L) and eAG (11.14 ± 2.7 mmol/L) was statistically significant ($p < 0.0001$) using the *t*-test and Mann-Whitney test for 2 independent groups. The correlation coefficient between FBS and eAG was r = 0.65 (95% CI; 0.62 - 0.69), with a p-value < 0.0001. These results are also shown in Figure 1.

In Table 2, the mean, standard deviation (SD), median, and interquartile range of HbA1c, eAG, and FBS values were calculated in 575 patients with type 2 diabetes mellitus with HbA1c levels lower than 6.5 mmol/L. The mean ± SD, median, and interquartile range of HbA1c were 5.9 ± 0.33%, 6.0% and 5.7 - 6.2%, respectively. The mean ± SD, median, and interquartile range for eAG were 6.84 ± 0.53 mmol/L, 6.9 mmol/L and 6.4 - 7.2 mmol/L, respectively. Similarly, the mean ± SD, the median, and interquartile range for FBS were 5.9 ± 1.15 mmol/L, 5.7 mmol/L and 5.3 - 6.3 mmol/L, respectively. The correlation coefficient between FBS and eAG at HbA1c < 6.5% was r = 0.251 (95% CI, 0.16 - 0.34), with a significant p-value of < 0.00001 (2-tailed test). Table 2 also shows the combined mean, standard deviation (SD), median, and interquartile range of eAG and FBS for all of the diabetic groups (n = 2,315), which were 10.1 ± 3.00 mmol/L, 9.5 mmol/L and 7.75 - 12.03 mmol/L for eAG, respectively. Similarly, these values were 8.5 ± 3.6 mmol/L, 7.5 mmol/L and 6.0 - 10.00 mmol/L for FBS, respectively.

DISCUSSION

In this study, we have shown that there is a positive correlation between FBS and eAG in adults with T2DM, which may have a major implication for the routine management of diabetic patients; however, there was a statistically significant difference. Unlike HbA1c, from which eAG is derived, FBS is an easy, quick, and cheap test to perform. Recently, during the time our study was conducted, a few studies confirmed similar findings. Bozkaya et al. reported using the same formula to show that eAG levels were closely associated with the FBS levels when the measurements were obtained on the same day [20]. They reported that determining a patient's HbA1c level might be unnecessary if they could determine the FBS level because they could simply calculate it with the formula. They reported that although their mean levels seemed to be similar, they were actually significantly different (p = 0.001), but this difference was not clinically meaningful. They also reported that the eAG and FBS values cannot be used interchangeably. They found that females had lower eAG and FBS levels than males. The decreased levels of eAG and HbA1c in women were significantly different from males. In addition, there was a significant difference between the eAG and FBS levels in both men and women (p < 0.0001). They concluded that patients with good to moderate blood glucose control were not entirely successful at managing their blood glucose, as reflected by their eAG levels, and the association between FBS and eAG levels depends on the extent of blood glucose control [20]. In another recent study, Ogbera et al. reported that there was a positive and significant correlation between HbA1c and FBS (r = 0.46, p = 0.0001) and HbA1c and fructosamine (r = 0.49; p = 0.0001) [21].

However, a few studies showed that there was discordance between HbA1c and mean blood glucose (MBG). Hempe et al. found discordance of glycemic control between eAG and MBG. In their study, MBG and HbA1c were recorded from the charts of 202 pediatric patients with type 1 diabetes who were divided into groups with low, moderate, or high HbA1c bias based on a hemo-

Table 1. The mean, standard deviation (SD), median, and interquartile range of HbA1c, eAG, and FBS for all patients with HbA1C (%) ≥ 6.5 (n = 1,740).

Lab test	Mean ± SD	Median	Interquartile range	r and p-value
HbA1C (%) > 6.5	8.64 ± 1.7	8.3	7.2 - 9.7	r = 0.24 p < 0.00001
eAG (mmol/L)	11.14 ± 2.7	10.60	8.8 - 12.8	r = 0.65 p < 0.00001
FBS (mmol/L)	9.3 ± 3.7	8.3	6.8 - 10.97	-

The r values were calculated for each parameter versus FBS.

Table 2. The mean, standard deviation (SD), median, interquartile range correlation coefficient (r) and p-values for HbA1c, eAG, and FBS for all patients with HbA1C (%) < 6.5 (n = 575).

Lab test	Mean ± SD	Median	Interquartile range	r and p-value
HbA1C (%) < 6.5 (n = 575)	5.9 ± 0.33	6.0	5.7 - 6.2	r = 0.0388; p < 0.00001
eAG (mmol/L)	6.84 ± 0.53	6.9	6.4 - 7.2	r = 0.251; p < 0.00001
FBS (mmol/L)	5.9 ± 1.15	5.7	5.3 - 6.3	NA
Combined group (n = 2,315) eAG	10.1 ± 3.0	9.5	7.75 - 12.03	r = 0.717; p < 0.00001
Combined group (n = 2,315) FBS	8.5 ± 3.6	7.5	6.00 - 10.00	NA

The r values of each parameter were calculated versus FBS.

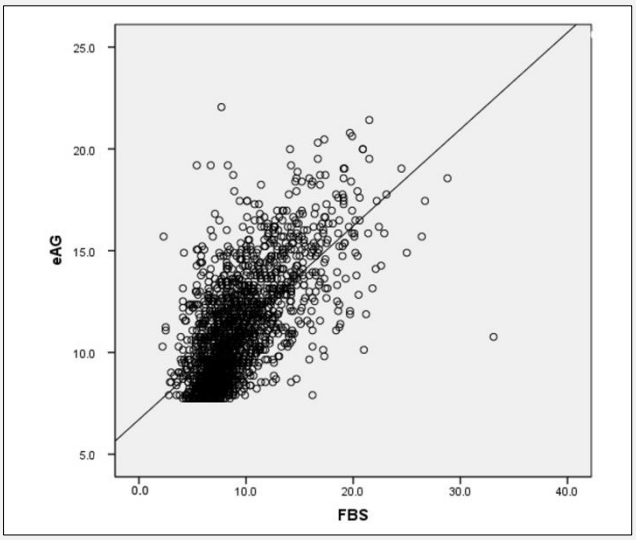

Figure 1. Correlation between fasting blood sugar (FBS) and estimated blood glucose (eAG), both in mmol/L.

hemoglobin glycation index (HGI), which was calculated as the difference between the observed HbA1c and the HbA1c predicted from the level of blood glucose. They concluded that eAG underestimated MBG in low-HGI patients and overestimated MBG in high-HGI patients [22]. Similar findings were reported by Chalew

et al., who found that there was a clinically significant disagreement between MBG and eAG in two pediatric populations [23].

Chen et al. reported that eAG might underestimate MBG in adult patients with T2DM and chronic kidney disease (CKD). However, their study had a small sample size and used self-monitored glucometers [24].

However, in some studies, agreement was achieved. Bouma et al. showed that FBS was fairly correlated with HbA1c [25,26]. In addition, other studies suggested that the predictive value of HbA1c was similar to FBS to monitor and predict secondary complications early in diabetic individuals [27]. This variation in HbA1c values was reported with values obtained in another laboratory using the same method [14,28,29]. However, this relationship was crude and has not been critically evaluated, and the authors reported that if a consistent and predictable relationship was found between FBS and eAG derived from HbA1c, then FBS could conceivably be used when HbA1c is not available or as a quick indicator of the overall control of diabetes mellitus [14,28,29].

Inoue et al. found that there was a significant correlation between the percentage of HbA1c and the mean levels of fasting blood sugar (FBS) during short intervals in patients with T2DM [30]. The measurement of HbA1c was concluded to be a useful method for evaluating the mean levels of blood glucose (MBG) during short intervals in patients with T2DM.

Woerle et al. found that both FBS and 2-hour post-challenge plasma glucose (PCPG) levels increased as HbA1c increased and were significantly correlated ($r = 0.63$, $p < 0.001$), but the 2-hour PCPG level increased at a 4 times greater rate than FBS and accounted for a greater proportion of HbA1c [31]. People who met the recommendations of the International Diabetes Federation (IDF) and American College of Endocrinology (ACE) HbA1c targets (< 6.5%) had significantly lower 2-hour PCPG levels than those who met the American Diabetes Association (ADA) target (< 7.0%) ($p = 0.03$), whereas FBS levels were similar [19,32].

Lack of standardization among HbA1c determination methods has led to wide lab-to-lab variation [33]. There is lab-to-lab variation even with the use of the same method. In many studies, the lab-to-lab variations in HbA1c values were reported with values performed in another laboratory using the same method [14,28,29]. However, these lab-to-lab variations were eliminated in HbA1c results in our study because all of the samples were analyzed on the same day and in the same lab. In addition, some HbA1c assay methods are unable to accurately measure HbA1c in individuals with common hemoglobin variants [34]. Behan et al. reported that HbA1c testing can be inaccurate in persons with elevated amounts of hemoglobin F or with abnormal hemoglobin, which can be found in the sickle cell trait, HbC trait, and HbE trait [35]. These variants are more prevalent in African and Asian Americans, the same demographic that has an increased risk of diabetes. Variant hemoglobins might cause a false increase or decrease in HbA1c, depending on the methodology and manufacturer. In a prospective cross-sectional study performed by Chandrasena et al. in Sri Lanka, they measured HbA1c in 2,695 T2DM subjects and found that 53 (2%) had abnormal hemoglobin types (HbF and HbS) [36]. They also reported that HbA1c concentrations in diabetic patients without Hb abnormalities show a higher correlation with fasting blood sugar (FBS) than those with hemoglobin abnormalities.

CONCLUSION

We concluded that there is a moderate and significant positive correlation between fasting blood sugar and the estimated average blood glucose derived from HbA1c. Although FBS might be helpful for daily monitoring of diabetes, further studies must be conducted to provide solid results to support that FBS can replace HbA1c and its derived variable eAG as an indicator of long-term overall control of T2DM patients.

However, there were some limitations in our study, which may include that it was performed in a retrospective manner. Additionally, the clinical circumstances of the patients were not known, which may affect the accuracy of the results. Last, the patient results that were obtained were not repeated for confirmation. We therefore recommend closely evaluating the relationship between eAG and FBS in a prospective case-control or cross-sectional study to extract more solid information.

Declaration of Interest:
The authors report no conflicts of interest.

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