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A Prospective Study of Correlation of Fructosamine with Continuous Glucose Monitor in Diabetic Patients

Gurdeep S[1]*, Anne S[2], Pablo C[1], Andreas F[1], Jennifer L[1], JoAnne E[1], Bridget A[1] and Timothy H[1]

[1]Our Lady of Lourdes Memorial Hospital-Ascension, Binghamton, USA
[2]Ascension Saint Agnes Hospital, Baltimore, USA

***Corresponding author:** Gurdeep Singh MD, Our Lady of Lourdes Memorial Hospital-Ascension 161 Riverside Drive, Binghamton, New York-13905, USA, Tel: 607-798-6701, Fax: 607-798-6164, Email: gurdeep.singh@ascension.org

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Abstract

Objective: To validate fructosamine for estimating the average glucose over a 2-week interval by comparing it with continuous glucose monitors.

Research Design and Method: In this prospective study, 129 patients with a history of diabetes mellitus type 1 or type 2 wore a continuous glucose monitor for 14 days. At the end of the study, blood work, including fructosamine, was performed and compared with the average glucose obtained from the continuous glucose monitor to validate the accuracy of fructosamine in estimating the average glucose. Bivariate Pearson correlation and Chi-square analyses and multivariable regression analyses were used to examine the linear relationships of the potential covariates of average glucose levels.

Results: The majority of participants was male (55.05%), caucasian (88.40%), and had type II diabetes (66.90%) with a mean age of 59.74 years (+15.44). The CGM devices used by these participants were made by Librepro (76.0%), Dexcom (16%), and Medtronic (8%). A binary logistic regression showed that those with a fructosamine value of 300mMol/L had 39% odds (95% CI 5.08 - 294.0) of having an average glucose value of < 200mg/dL, P < .001. Iterative Chi-square analyses showed that for patients having a fructosamine threshold of 300mMol/L or less, 98% had a CGM determined average glucose value of < 200mg/dL.

Conclusion: When the serum fructosamine is less than 300μmol/L, the average glucose over the previous two weeks is less than 200mg/dL in 98% of patients.

Keywords: Diabetes Mellitus; Diabetes; Glycemic Control

Abbreviations: DM: Diabetes Mellitus; CGM: Continuous Glucose Monitor; CV: Coefficient of Variation.

Introduction

Diabetes mellitus (DM) is a disease caused by the pancreas' inability to produce an appropriate amount of insulin or the body's inability to use the insulin produced effectively [1]. The resultant hyperglycemia has been shown in multiple studies to increase the risk of micro vascular and macro vascular complications in people with diabetes [2-6]. Achievement and maintenance of good glycemic control is therefore a critical goal in diabetes management [2-6].

Although hemoglobin A1C is the best validated assessment of long-term glycemic control [4,7,8], there are important clinical scenarios where a shorter-term estimate of glycemic control is needed. For example, in red blood cell disorders, or in situations with rapid changes in glucose homeostasis [4,9-11], A1C does not accurately reflect recent glycemic control. The limitations of A1C present an opportunity for alternate glycemic markers, such as fructosamine, to be of clinical use in monitoring glycemic control [12-16]. Fructosamine's shorter half-life may reflect average glucose changes over 2-3 weeks, in contrast to the 120 days required for A1C to stabilize. Unfortunately, fructosamine's lack of standardization for estimating the average glucose has greatly limited its clinical utility. This objective of this study is to validate fructosamine for estimating the average glucose over a 2-week interval by comparing with average glucose obtained from continuous glucose meter.

Methods

Patient Selection

This prospective study required participants to wear a continuous glucose monitor (CGM) for 14 days. At the end of the study period, the CGM data was downloaded. Participants included both men and women between ages 18 and 90 years, who carried a diagnosis of either Type I or Type II Diabetes Mellitus. All participants were patients at an adult endocrinology practice. Participants were excluded if there was more than a 48-hour gap during the CGM data collection period. Being on an anti-hyperglycemic medication was neither an inclusion nor exclusion criterion.

Sample Size Considerations

Given that this is an exploratory analysis of the relationship between fructosamine and average glucose levels, we developed sample size estimates based on effect size, that being the correlation of fructosamine and average blood glucose. At a 2-tailed probability of 0.05, and the probability of failing to reject the null hypothesis under the alternative hypothesis set at .20, and the minimal correlation of fructosamine to average blood glucose at 0.4, the study was determined to require at least 46 paired observations of CGM glucose levels and fructosamine levels.

Demographic and Laboratory

The collected data included the participant's age, gender, ethnicity, type of diabetes mellitus, CGM type, mean glucose level with SD and percent coefficient of variation (CV), fructosamine, hemoglobin A1C, hemoglobin, hematocrit, GFR, and albumin. If not available from download, the CV was calculated as the SD of daily blood glucose levels divided by the mean glucose value times 100.

The following CGMs were utilized: Guardian Connect by Medtronic, Dexcom G6, and Freestyle Libre. The choice of which CGM to use was based on insurance coverage. Data from the 14 day study interval was downloaded during office visits between January 2019 and March 2020. Fructosamine was analyzed by ARUP Laboratories using the Roche Cobas c702 with a percent CV of 1.0 (laboratory reference range 170-285µmol/L). Hemoglobin A1C was either analyzed with the Abbott Alinity c Hemoglobin A1C assay, or the Ortho Clinical Diagnostic Vitros 5600 Integrated System. Both laboratories used a reference range of 4-14%. Institutional review board approval was obtained before the study's commencement, with each participant signing the Agreement to Participate in A Research Study Medical Research Informed Consent form.

Statistical Approaches

Univariate statistical approaches (frequency distributions and analyses of normality) were used to describe the demographic and clinical features of the patients from whom fructosamine levels were measured. Data found to be normally distributed were subjected to parametric statistics; otherwise, data were analyzed using non-parametric analyses. Given that few hematocrit values were available (n=6), this measure was excluded from the binary logistic regressions.

Bivariate Pearson correlation and Chi-square analyses and multivariable regression analyses were used to examine the linear relationships of the potential covariates of average glucose levels. Potential confounders were stratified into normal and abnormal ranges to discern if abnormal ranges were associated with higher fructosamine values; normal hemoglobin was considered to be from 12-16g/dL, normal hematocrit 36-47%, normal albumin 3.5-5g/dL and normal GFR > 60mL/min/1.73m^2. Covariates showing no correlative strength with CGM glucose were removed from the linear regression analyses in a backward elimination fashion. Iterative sensitivity analyses, i.e., multiple Chi-square analyses, were used to find the optimum threshold of fructosamine that gave the best specificity for predicting glucose values of < 200mg/dL.

Results

The majority of participants was male (55.05%), caucasian (88.40%), and had type II diabetes (66.90%) with a mean age of 59.74 years (+ 15.44) (Table 1). The CGM devices used by these participants were made by Librepro (76.0%), Dexcom (16%), and Medtronic (8%).

Age	59.74 ± 15.44	
Gender	Male	71 (55.05%)
	Female	58 (44.95%)
Ethnicity	White	114 (88.4%)
	Black	5 (3.9%)
	Asian	7 (5.4%)
	Hispanic	2 (1.6%)
	Other	1 (0.8%)
DM Type	1	42 (33.1%)
	2	85 (66.9%)
CGM Type	Dexcom	27 (21.8%)
	LibrePro	97 (78.2%)
Laboratory Values		
Mean ± SD		
	Fructosamine	329.25 ± 66.51
	CV	32.37 ± 9.38
	SD	59.04 ± 24.39
	A1C	8.13 ± 1.27
	Albumin	3.78 + 0.26

Table 1: Demographic, Clinical and Laboratory Features of Study Population.

As shown in Table 2, binary logistic regressions models were constructed that first contained all potential confounders of fructosamine levels and normal/abnormal designations for hematocrit, GFR, albumin, and hemoglobin. These possible confounders were collected within 2 days of CGM download and none of these potential confounders were found to be statistically impactful on CGM glucose levels, as evidenced by their p-values of > .05 and 95% CIs that include 1. After the removal of potential confounders, binary logistic regression showed that those with a fructosamine value of 300mMol/L had 39% odds (95% CI 5.08 - 294.0) of having an average glucose value of < 200mg/dL, P < .001 (Table 3).

Variables in the Equation					
		Significance	OR	95% C.I. for OR	
				Lower	Upper
Step 1[a]	hemoglobin	0.861	1.34	0.051	35.312
	GFR	0.698	1.622	0.141	18.694
	albumin	0.191	7.682	0.362	163.224
	Fructosamine ≤ 300	0.998	1669909974	0	.
	Constant	0.998	0		

a. Variable(s) entered on step 1: hemoglobin2, GFR2, albumin2, fruc_grp300.

Table 2: Regression of potential confounders to average CGM Glucose.

Variables in the Equation					
		Significance	Odd's ratio	95% C.I.for OR	
				Lower	Upper
Step 1[a]	Fructosamine ≤ 300	<.001	38.636	5.077	294.012
	Constant	<.001	0.001		

a. Variable(s) entered on step 1: fructosamine < 300.

Table 3: Shows that the reduction of covariates to those that significantly predict CGM glucose, i.e., fructosamine, CGM glucose can be estimated by multiplying fructosamine by 0.568 or 0.57.

In our sample, iterative Chi-square analyses showed that for patients having a fructosamine threshold of 300mMol/L or less, 98% had a CGM determined average glucose value of < 200mg/dL (Table 4).

P < .001		glucose group		Total
		< 200mmol/L	≥ 200mmol/L	
Fructosamine	≤ 300mmol/L	50	1	51
		98.00%	2.00%	100.00%
	> 300mmol/L	44	34	78
		56.40%	43.60%	100.00%
Total		94	35	129
	% within fructosamine_group 300	72.90%	27.10%	100.00%

Table 4: Specificity of HbA1C and Fructosamine in predicting Average CGM Glucose.

Discussion

Fructosamine is a glycated ketoamine discovered over 35 years ago. It can be measured inexpensively, precisely, and relatively free of interference [16,17]. It can be automated for use with micro-sample volumes [17]. Fructosamine is relatively unaffected by RBC diseases, making it attractive as a suitable glycemic marker for people affected by RBC abnormalities such as sickle cell disease/trait. Compared to alternate measures of average glucose, its lower cost makes it more accessible to populations with limited resources [17], In our prospective study, we found that fructosamine has a strong relationship with average glucose as determined by continuous glucose measurement. Multiple Chi-square analysis showed that 98% of patients having a fructosamine of 300mMol/L or less had a CGM estimated 2-week average glucose of less than 200mg/dL.

There are several scenarios where this estimate of the average glucose would be clinically important. In the assessment of operative risk, knowing the average glucose is less than 200 immediately prior to scheduled surgery verifies that diabetes is under good control and thereby does not represent an increased risk for an untoward surgical outcome. For example, a recent study by Shohat et al found that preoperative fructosamine value of ≥ 292µmol/L had a significant correlation with deep infection in patients undergoing total hip and knee arthroplasty [18].

For patients with previously uncontrolled diabetes undergoing medication adjustment to get their blood sugar under control, documenting a clinical response over two weeks rather than waiting three months for the A1C to change would be useful. Although frequent point of care capillary glucose measurements can provide a reasonable estimate of average glucose, for many patients this approach is either unacceptable or not feasible. When compared to the use of a continuous glucose measurement study to establish average blood sugar control, fructosamine is substantially more convenient, quicker, and less costly.

There may be circumstances where a more precise estimate of the average glucose is needed. When the fructosamine is less than 300mg/dL (average glucose < 200mg/dL), the average glucose can be estimated: Fructosamine x 0.57=average glucose (Table 3). Unfortunately, when the fructosamine is greater than 300mMol/L, its relationship to the CGM estimated average glucose becomes unpredictable. A similar weakness is shared by the hemoglobin A1C, where it has been shown that when the A1C exceeds 8% there is no statistical correlation with the CGM-assessed average glucose [19].

Clinical conditions that affect protein metabolism such

as nephrotic syndrome, thyroid disease, and liver disease may have an influence on fructosamine level and its ability to accurately assess average glucose [4]. We did not find any impact of albumin on fructosamine's ability to predict average glucose. We also did not find any impact of the standard deviation of coefficient of variation on fructosamine.

We are not aware of any prior study of more than 100 subjects that evaluated the correlation between fructosamine and CGM determined average BG level. Limitations of this study include lack of diversity, with the caucasian population comprising 88.4% of total participants. Potentially confounding factors, such as creatinine, hemoglobin, hematocrit albumin were not available in 50-65% of cases at the time of download.

Conclusion

On occasions where the short-term determination of average blood sugar control is important, and alternative assessment strategies are not feasible, serum fructosamine is a convenient, cost-effective, and reliable option. Knowing that the average serum glucose is less than 200mg/dL in 98% of patients with a fructosamine of less than 300mMol/L provides useful and reliable information that can significantly improve decision making in a variety of clinical situations.

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