ORIGINAL ARTICLE

Correlation between Serum Fructosamine and Self-Monitoring Blood Glucose in Patients with Diet-Controlled Gestational Diabetes Mellitus

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Objective: To determine the correlation between serum fructosamine and self-monitoring blood glucose (SMBG) levels in gestational diabetes mellitus (GDM) patients treated by dietary control and to identify the cutoff level of serum fructosamine for determining poorly controlled GDM.

Materials and Methods: A cross-sectional study conducted between October 2021 and August 2022 at Queen Savang Vadhana Memorial Hospital that included 78 singleton pregnancies diagnosed with GDM assigned to diet therapy with lifestyle modification. The daily home SMBG was performed following the standard protocol and the serum fructosamine was measured one month after starting dietary control. The correlation between serum fructosamine and means of SMBG were analyzed. The receiver operating characteristics (ROC) curve was plotted to identify the cutoff level of serum fructosamine for predicting poorly controlled GDM based on SMBG levels. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the cutoff level were calculated.

Results: The correlation between serum fructosamine and SMBG were 0.436 ($p<0.001$) and 0.618 ($p<0.001$) in pre-prandial and post-prandial glucose levels, respectively. The poorly controlled SMBG group had serum fructosamine greater than the well-controlled group with a mean of 165.7±35 and 132.8±23 µmol/L ($p<0.001$). The ROC curve showed that using 160 µmol/L as the optimal cutoff level to determine poorly controlled GDM had 72.7% sensitivity, 88% specificity, 50% PPV, 95.2% NPV, and 85.9% accuracy.

Conclusion: The serum fructosamine was very useful for monitoring dietary control of GDM in terms of drawing blood less frequently, convenient, and more economical. An optimal cutoff point for screening a poorly controlled GDM was 160 mol/L.

Keywords: Gestational diabetes mellitus; Serum fructosamine; Self-monitoring blood glucose

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Gestational diabetes mellitus (GDM) is one of the most common complications in pregnant women. Poorly controlled GDM leads to negative effects on mothers, fetuses, and neonates including preeclampsia, cesarean birth, fetal large for gestational age, hydramnios, shoulder dystocia, perinatal asphyxia, and stillbirth[1,2]. It is therefore essential to maintain optimal blood glucose levels during pregnancy. Self-monitoring blood glucose (SMBG) is the standard method used for monitoring blood glucose levels in GDM[1,2]. A significant advantage of SMBG is that abnormal values can be clearly identified within each meal, making it possible to adjust insulin doses precisely. However, one of the disadvantages of SMBG is that patients are required to draw blood from their fingertips several times a day, which may be uncomfortable and inconvenient. Additionally, the cost is quite high, and the blood glucose levels are often affected by food intake from meal to meal[3,4].

Research over the past twenty years has shown that there are other laboratory tests can be used for monitoring glucose levels in patients with diabetes such as serum fructosamine, hemoglobin A1c (HbA1c), glycated albumin and 1,5 A-hydroglucitol[3]. Serum fructosamine can reflect the levels of glucose molecules bound to albumin in the blood during the preceding two to four weeks[3-6]. In previous studies, serum fructosamine levels have been shown to be

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closely correlated with random blood glucose[5], fasting blood glucose[7], HbA1c levels[5,8], and glucose challenge test (GCT)[9]. Serum fructosamine also provides advantages such as being easily accessible, inexpensive, and having less daily fluctuation[3-6]. Moreover, serum fructosamine does not vary in each trimester of pregnancy[10] and it is less affected by red blood cell disorders that can be found in thalassemia[3-6] and iron deficiency anemia[3]. However, the serum fructosamine level may be lower than normal in some conditions such as dilutional anemia[1,11], inflammatory process, hyperthyroidism, and kidney and liver dysfunction that interfere with albumin metabolism[3-6].

There are few prospective studies on the correlation between serum fructosamine levels and the mean levels of SMBG in type 1[12] and type 2[13,14] diabetes mellitus patients, but no previous studies have focused on this correlation in GDM patients. Therefore, the present study aims to determine the correlation between serum fructosamine and SMBG in GDM patients treated with dietary control, and to define the cutoff level of serum fructosamine to identify the patients with poor glycemic control.

Materials and Methods

Study design and participants

The present was a cross-sectional study conducted between October 2021 and August 2022 at Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand. The study protocol was approved by the Institutional Review Board of Queen Savang Vadhana Memorial Hospital, IRB number 041/2022. Pregnant women who attended the antenatal care unit were asked to participate in the present study.

The inclusion criteria were 1) age between 18 to 34 years, 2) singleton pregnancy, 3) 24 to 36 gestational weeks, 4) patients diagnosed with GDM based on risk-based screening using Carpenter and Coustan criteria[1] and assigned to dietary control, 5) pregnant women with no established type 1 or 2 diabetes mellitus. Exclusion criteria included participants with high blood glucose levels of more than 250 mg/dL, those who required medication control, and those with hypoalbuminemia, liver, kidney, or thyroid conditions[3]. Blood tests were not performed on all participants, but their medical histories were taken into consideration. To ensure the accuracy and reliability of SMBG data collected by participants, we excluded participants who had no follow up and those who did SMBG tests less frequently than 80% of the time within two weeks.

The sample size was calculated using correlation coefficient formula[15], r=0.347[12], setting the type I error and power to 5% and 90%, respectively, and allowing for a 10% dropout rate. Therefore, the estimated sample size required was 83 participants.

Procedure

After completion of the informed consent process, an extensive history taking was performed on each participant included their age, parity, gestational age, underlying diseases, current medications, and risks associated with antenatal care. A pre-pregnancy body mass index (BMI), the hemoglobin in the first visit, and a 100 g oral glucose tolerance test (OGTT) values were also recorded. All participants were advised for dietary modifications, and nutritional instructions of three daily meals and snacks according to their adjusted body weight by the nutritionist and were prescribed supplements of iron, calcium, iodine, and folic acid.

All participants were in accordance with SMBG standard protocol that required measurements and records of fingertip blood glucose four times per day, before breakfast, one hour after breakfast, one hour after lunch, and one hour after dinner. Then the results were reviewed by an endocrinologist every two weeks for glycemic status assessment. The well controlled group was defined as greater than or equal to 70% of the SMBG measurements and achieved the target level as pre-prandial at less than 95 mg/dL and one hour post-prandial of three meals at less than 140 mg/dL. and the poorly controlled group was defined as SMBG measurements reached the target level less than 70% of the time. The primary outcome measure was the random serum fructosamine level at one month after initiation of dietary control using the CH930 Atellica™ Solution, a chemistry analyzer equipped with electrolyte testing and photometric testing capabilities. The participants who were prescribed glucose-lowering medicines were excluded.

Statistical analysis

The data were analyzed using IBM SPSS Statistics, version 28.0 (IBM Corp., Armonk, NY, USA). Numerical variables were presented as mean ± standard deviation (SD), and categorical variables were presented as number (n) and percentage (%). Comparison of numerical and categorical variables were performed using student's t-test and chi-square test, respectively. The Pearson correlation coefficient (r) was measured to determine the strength

Table 1. Comparison of demographic characteristics between the well-and poorly controlled groups

Demographic characteristics	Well controlled (n=67)	Poorly controlled (n=11)	p-value
Maternal age (years); mean±SD	30.5±2.9	30.1±4.1	0.668
Parity; n (%)			1.000
<3	65 (97.0)	11 (100)	
≥3	2 (3.0)	0 (0.0)	
Gestational age at diagnosis of GDM (weeks); mean±SD	27.2±2.9	27.9±3.3	0.472
Pre-pregnancy BMI (kg/m^2); mean±SD	25.0±5.1	29.5±5.9	0.010*
Dilutional anemia; n (%)	2 (3.0)	0 (0.0)	0.559
Underlying diseases; n (%)			0.308
No	57 (85.1)	8 (72.7)	
Yes (CHT, Thalassemia trait, Chronic HBV infection)	10 (14.9)	3 (27.3)	

SD=standard deviation; GDM=gestational diabetes mellitus; BMI=body mass index; CHT=chronic hypertension; HBV=hepatitis B virus
* p<0.05, statistically significance

and direction of the relationship between serum fructosamine levels and the mean levels of SMBG. A p-value less than 0.05 was considered statistically significant.

The receiver operating characteristics (ROC) curve was plotted and the area under the curve (AUC) was calculated to demonstrate the optimal cut point of serum fructosamine for screening poorly controlled GDM, which was the point on the ROC curve that provided the best AUC. Based on the two-by-two tables, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were also calculated.

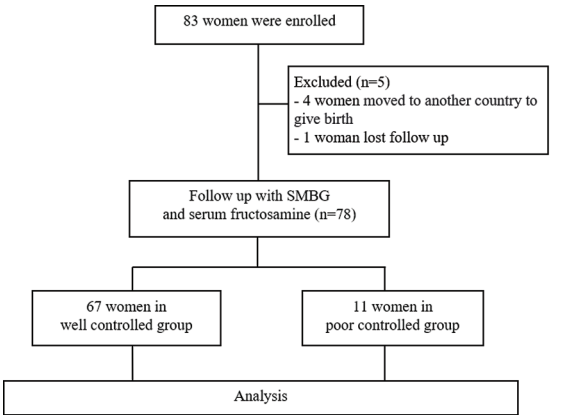

Figure 1. Study flowchart.

Results

The present study included 83 patients with diet controlled GDM. However, five were excluded from the present study as four relocated to another country and one was lost to follow-up. Within two weeks, no participants were excluded due to poor compliance of SMBG tests less than 80% of the time. Therefore, 78 participants were analyzed into two groups, a well-controlled group with 67 participants and a poorly controlled group with 11 participants (Figure 1). The results in Table 1 demonstrated demographic characteristics between the two groups and found that only the mean of pre-pregnancy BMI was significantly higher in the poorly controlled group (p=0.010). Among these participants, four in well control group and two in poor control group had chronic hypertension treated with methyldopa and aspirin, five in the well control group and three in the poor control group had thalassemia trait, and one in the well control group had chronic hepatitis B virus infection. The mean of serum fructosamine levels was found to be significantly higher in the poorly controlled group compared with well controlled group at 165.7±35 versus 132.8±23 µmol/L, respectively (95% CI 16.8 to 49.1, p<0.001) (Table 2).

The result from Pearson correlation analysis showed the serum fructosamine level was significantly correlated with the mean levels of pre- and post-prandial SMBG, with Pearson's correlation coefficient (r) of 0.436 (p<0.001) and 0.618 (p<0.001), respectively (Table 3). Regarding ROC curves analysis, the ability of serum fructosamine to predict poorly controlled GDM had AUC of 0.786 (95% CI 0.589 to 0.983, p=0.002) (Figure 2). The optimal level of serum fructosamine to screen poorly controlled GDM was 160 µmol/L. This cutoff level presented 72.7% sensitivity, 88% specificity, 50% PPV, 95.2% NPV, and 85.9% accuracy (Table 4).

Discussion

Serum fructosamine level and SMBG were significantly correlated, especially the postprandial SMBG. Compared to previous studies, serum

Table 2. Comparison of serum fructosamine and means of preprandial and postprandial SMBG levels between well-and poorly controlled groups

Serum blood sugar	Well controlled (n=67)	Poorly controlled (n=11)	p-value	95% CI
Serum fructosamine level (umol/L)	132.8±23.2	165.7±34.5	<0.001	16.8 to 49.1
Mean preprandial SMBG (mg/dL)	84.9±7.4	112.7±31.9	<0.001	19.0 to 36.5
Mean postprandial SMBG (mg/dL)	120.1±8.5	160.5±17.9	<0.001	33.7 to 47.0

CI=confidence interval; SMBG=self-monitoring blood glucose

Table 3. Correlation between serum fructosamine and the mean levels of preprandial and postprandial SMBG

Correlation		Mean levels of preprandial SMBG	Mean levels of postprandial SMBG
Serum fructosamine levels	Pearson correlation coefficient (r)	0.436	0.618
	p-value	<0.001*	<0.001*
	n	78	78

SMBG=self-monitoring blood glucose
* p<0.05, statistically significance

Table 4. Sensitivity, specificity, PPV, NPV and accuracy in each cutoff level of serum fructosamine to identify poorly controlled GDM

Cutoff level of serum fructosamine (μmol/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
150	72.7	81.4	44.4	95.0	83.3
160	72.7	88.0	50.0	95.2	85.9
165	62.5	94.3	55.6	95.7	91.0
170	45.5	98.5	83.3	91.7	91.0

PPV=positive predictive value; NPV=negative predictive value

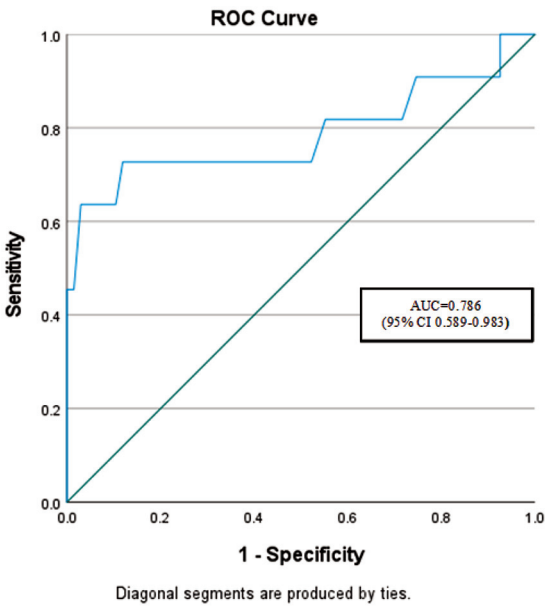

Figure 2. ROC curve illustrates the ability of serum fructosamine to predict poorly controlled GDM based on SMBG levels.

fructosamine can effectively provide insights into glycemic load over the preceding two weeks, particularly in the context of postprandial glucose monitoring. Serum fructosamine has been statistically correlated with random blood glucose[5], fasting blood glucose[7], HbA1c[5,8], and mean levels of SMBG in both type 1[12] and type 2[13,14] diabetic patients. However, prior research in this field was dated, and there are methodological concerns that need to be addressed. A correlation between serum fructosamine level and SMBG has not yet been established in any studies of patients with GDM. Furthermore, no study has been performed to determine the cutoff level of serum fructosamine in classifying GDM patients of well controlled or poorly controlled glycemic control. From the present study, the cutoff of 160 μmol/L (AUC 0.786, 95% CI 0.589 to 0.983, p=0.002) provides the high accuracy to determine glycemic status with 72.7% sensitivity, 88% specificity, 50% PPV, 95.2% NPV, and 85.9% accuracy.

The present study found that pre-pregnancy BMI was significantly correlated with poorly controlled SMBG in obese individuals, which is consistent with insulin resistance in this population. As the outcome was not compared between the two groups, but calculated individually, it was not considered a confounding factor. Several participants in the present study had chronic hypertension, thalassemia, and chronic hepatitis B virus infection, but based on the

literature reviews, none of these conditions affected serum fructosamine levels, so they did not contribute to confounding factors. Although hypoalbuminemia, liver, kidney, and thyroid disorders may have confounded the results, these conditions were excluded based on a thorough history taking process, in order to ensure that the results would be properly interpreted. In addition, previous research had shown that dilutional anemia affected serum fructosamine as well[3]. Two participants in the present study had dilutional anemia, which was diagnosed through the first and second blood results of antenatal care. Although they were able to control their SMBG well, their fructosamine level was high at 166,180 μmol/L. Therefore, dilutional anemia may result in falsely high serum fructosamine levels.

The strength of the present study lies in its analytical design, and it is the first study to determine correlation and cutoff level between serum fructosamine and SMBG levels in GDM patients as a means of discriminating glycemic control status, which will allow the development of new guidelines for treatment and follow-up of patients with GDM. The limitations to the present study include the small number of participants in the poor control group compared to the well control group, which may limit its validity. Furthermore, the present study was a cross-sectional study, so it cannot provide long-term insights into maternal and neonatal outcomes. Lastly, the results of the present study were inapplicable to patients' requiring insulin because there are currently no guidelines for adjusting insulin dosage, which can have adverse effects on babies and mothers if glucose levels were excessive. In the current situation, if the patient was found to have fructosamine levels in the poor glucose control group, it is still necessary to refer the patient to SMBG for further treatment. However, patients who are able to control their glucose well can be excluded, which is advantageous in terms of reducing treatment costs and improving convenience.

The present study is only a preliminary study, and further studies should be done with a larger number of participants to ensure validity of the study's conclusions. In addition, longitudinal studies would provide robust evidence of the relationship between these variables and allow for analysis of changes over time. Furthermore, a study should be conducted comparing maternal and neonatal outcomes when monitoring GDM with serum fructosamine versus standard SMBG levels. A study could also be conducted to establish standard levels of fructosamine for use in adjusting insulin dose every two to four weeks, enabling serum fructosamine to be used in place of SMBG without adversely affecting clinical outcomes.

Conclusion

Serum fructosamine was very useful for monitoring dietary control of GDM in terms of drawing blood less frequently, convenient, and being more economical as it only needs follow-up every two weeks. Nevertheless, the time to follow-up is not too long to adjust the treatment. An optimal cutoff point for screening a poorly controlled GDM is 160 μmol/L.

What is already known on this topic?

A statistical correlation exists between serum fructosamine levels and SMBG levels for type 1[12] and type 2[13,14] diabetic patients, but a similar correlation has not been established in studies of patients with GDM. In addition, no study has been performed to determine the cutoff level of serum fructosamine in classifying GDM patients as well controlled or poorly controlled.

What does this study add?

Significant correlations were found between serum fructosamine levels and SMBG levels. The serum fructosamine level of 160 μmol/L can be used to screen poorly controlled GDM instead of SMBG as a glycemic control indicator.

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Conflicts of interest

The authors declare no conflict of interest.

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