PAIRED VALUES OF SERUM FRUCTOSAMINE AND BLOOD GLUCOSE FOR THE SCREENING OF GESTATIONAL DIABETES MELLITUS: A RETROSPECTIVE STUDY OF 165 SAUDI PREGNANT WOMEN

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ABSTRACT

This study reports the utilization of serum fructosamine and blood glucose for the screening of gestational diabetes mellitus (GDM). Blood samples from 165 pregnant women were analyzed for fasting blood glucose (FBG), random blood glucose (RBG) and serum fructosamine. The actual fructosamine levels were corrected for serum protein (c-Fruct) for more precise presentation. Two cut-off values of FBG (>5.3 mmol/L and >7.0 mmol/L) and RBG (>7.8 mmol/L and >11.0 mmol/L) were used to classify hyperglycemic subjects for subsequent evaluation. The average values $\pm$ standard deviations for FBG, RBG and cFruct were 5.865 ± 1.95 , 7.767 ± 3.21 and 2.387 ± 0.47 mmol/L, respectively. FBG levels were significantly correlated with RBG (Pearson correlation = 0.597, $P < 0.001$). Significant correlations were also observed between cFruct and FBG (Pearson correlation = 0.673, $P < 0.001$) or RBG (Pearson correlation = 0.641, $P < 0.001$). Out of 165 subjects, 24 (14.5%) cases were classified as hyperglycemic on the basis of FBG >7.0 mmol/L or RBG >11.0 mmol/L; use of lower cut-off values resulted higher frequencies of hyperglycemia. Whereas, a combined criteria of FBG >5.3 mmol/L and cFruct >2.5 mmol/L predicted 35 patients as the most probable hyperglycemic as compared to 32 patients identified using the criteria of RBG >7.8 mmol/L and cFruct >2.5 mmol/L. These criteria were associated with 4.8% and 3.6% false-positivity at the expense of 3.6% and 3.0% false-negative outcomes, respectively. The levels of FBG, RBG and cFruct were significantly higher in hyperglycemic groups (irrespective of grouping criteria) as compared to the respective normal groups. In conclusion, these findings clearly indicate that the paired values of cFruct with FBG or RBG could help in filtering high-risk individuals for OGTT and therefore avoiding a unnecessary OGTT.

KEY WORDS

Gestational diabetes mellitus; Serum fructosamine; Fasting blood glucose; Random blood glucose

INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disorder and a common medical complication during pregnancy. GDM is associated with adverse fetal and maternal outcomes that can be prevented by timely diagnosis and management of GDM (1). Routine screening for GDM is therefore an important

aspect of antenatal care in order to minimize its serious consequences. Oral glucose tolerance test (OGTT) is considered as the gold standard for the diagnosis of GDM (2), although its reliability has also been questioned (3). The routine application of OGTT for screening of GDM is hampered by its high cost, lengthy procedure and patients' noncompliance. Simple approaches are therefore sought to minimize the use of OGTT without compromising the likelihood of diagnosing GDM. A mini version of OGTT, known as glucose challenge test (GCT) has been widely used for the screening of GDM. Rey et al (4) concluded that 1-h, 50-g GCT is a sensitive test for the prediction of GDM, whereas Lani and Barrett (5) reported the poor performance of the same test for the diagnosis of GDM. In fact, there are no fixed criteria for GCT and variable cut-off values have been used to achieve

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acceptable sensitivity and specificity (6,7). On the other hand, fasting blood glucose (FBG) (8) and random blood glucose (RBG) (9,10) are the simplest and commonly used tests for the (pre)screening of GDM.

Measurement of glycated proteins including fructosamine (11) and glycated hemoglobin (HbA1c) (12) has been employed for the assessment of short- and long-term glycemic control, respectively. Determination of serum fructosamine is a fully-automated, simple, sensitive and reproducible method for the evaluation of glycemic control (13). Since fructosamine determines the average glucose over the past 2-3 weeks the test is not affected by the food eaten during the day. Serum fructosamine levels did not differ significantly if measured at fasting or 2 h after ingestion of 75 g glucose (14). For this reason fructosamine can be measured at any time during the day. The use of serum fructosamine for the screening of GDM has been widely reported (15-19). A single fructosamine test compared to GCT has given a sensitivity of 87.5% and specificity of 94.5% for the detection of GDM (20). Salemans et al (21) have noticed that fructosamine is more sensitive than HbA1c for the detection of abnormal glucose tolerance. Serum fructosamine has been correlated with FBG (22,23), OGTT (18) and HbA1c (16). This investigation was aimed to find out a possible association between serum fructosamine and FBG or RBG, and the usefulness of the paired values of fructosamine with FBG or RBG for filtering the high risk patient towards screening the GDM.

MATERIALS AND METHODS

A total of 165 Saudi pregnant women attending the antenatal care clinics at the Armed Forces Hospital, Riyadh during the years 2003-2004 were included in this study. Venous blood samples were collected from all the subjects after at least 8 h fasting for the analysis of FBG, whereas the blood samples from the non-fasted subjects were collected for the analysis of RBG and serum fructosamine.

All the three biochemical parameter were analyzed by using an Autoanalyzer (Roche Modular P-800, Germany). The actual fructosamine levels were corrected for serum protein to give corrected-fructosamine (cFruct) for more precise presentation (22,24,25). Two cut-off values of FBG (>5.3 mmol/L and >7.0 mmol/L) and RBG (>7.8 mmol/L and >11.0 mmol/L) were used to classify hyperglycemic subjects. A reference range of cFruct between 1.8 - 2.5 mmol/L was used on the basis of earlier reports (13,19).

The data were evaluated by SPSS statistical package version 10. Pearson's correlation test was performed to analyze an association between c-Fruct and FBG or RBG. Independent samples Student's t-test (2-tailed) was used to compare means between the normal and hyperglycemic groups, categorized using specified criteria. *P* values less than 0.05 were considered as statistically significant.

Fig. 1. Correlation between corrected fructosamine and (a) fasting blood glucose (Pearson correlation = 0.673, $P < 0.001$) and (b) random blood glucose (Pearson correlation = 0.641, $P < 0.001$).

Table 1 : Levels of fasting blood glucose (FBG), random blood glucose (RBG) and corrected fructosamine (cFruct) in 165 pregnant women.

Biochemical test (mmol/L)	Mean	Standard deviation	Minimum	Maximum
FBG	5.865	1.951	3.10	15.40
RBG	7.767	3.210	3.60	21.70
cFruct	2.387	0.478	1.68	4.41

RESULTS

The levels of FBG, RBG and c-Fruct in 165 pregnant women were found to be 5.865 mmol/L, 7.767 mmol/L and 2.387 mmol/L respectively (Table 1). A significant correlation was observed between FBG and RBG (Pearson correlation = 0.597, $P < 0.001$). Both FBG (Pearson correlation = 0.673, $P < 0.001$) and RBG (Pearson correlation = 0.641, $P < 0.001$) were also significantly correlated with cFruct (Fig. 1).

Using the FBG cut-off >5.3 mmol/L, 81 subjects were classified as hyperglycemic; this frequency reduced to 24 subjects when a FBG cut-off >7.0 mmol/L was used (Table 2). However, among these 24 subjects (who had FBG >7.0 mmol/L), 5 patients had incompatible RBG (≤ 7.8 mmol/L) or cFruct (≤ 2.5 mmol/L) levels. Using the RBG cut-off >7.8 mmol/L, 62 subjects were classified as hyperglycemic, whereas a high the cut-off value of RBG >11 mmol/L reduced the number of hyperglycemic subjects to 24 (Table 2). Of these 24 subjects, 7 subjects showed incompatible FBG (≤ 5.3 mmol/L) or cFruct (≤ 2.5 mmol/L) levels. The levels of FBG, RBG and cFruct were significantly higher in hyperglycemic groups (irrespective of grouping criteria) as compared to the respective normal groups (Table 2).

Fig. 2. Schematic presentation of using paired values of (a) FBG >5.3 mmol/L and cFruct >2.5 mmol/L or (b) RBG >7.8 mmol/L and cFruct >2.5 mmol/L for filtering high risk individuals (suspected GDM). The values within rectangles are number of subjects.

Figure 2 shows the application of combined values of cFruct and FBG or RBG for filtering the high risk subjects with a fair probability of GDM. Out of 165 patients, 35 were identified as the most probable hyperglycemic on the basis of combined criteria of FBG > 5.3 mmol/L and cFruct > 2.5 mmol/L. Eight patients among these 35 had RBG $\leq$ 7.8 mmol/L and hence categorized as false-positive (4.85%). Whereas, 6 out of 84 subjects who had FBG $\leq$ 5.3 mmol/L also showed RBG > 11.0 mmol/L and recognized as false-negative (3.64%) (Fig. 2a). On the other hand, using the combination of RBG > 7.8 mmol/L and cFruct > 2.5 mmol/L, 32 patients were categorized as hyperglycemic while 5 subjects each appeared to be false-positive (3.0%) and false-negative (3.0%) (Fig. 2b). Twenty seven (84.4%) of these 32 patients were common to the filtered patients while using the FBG plus cFruct criteria.

Table 2. Characterization of glycemic status using specific cut-off values of FBG and RBG.

Criteria	Number of subjects	Glycemic status	FBG (mmol/L)	RBG (mmol/L)	cFruct (mmol/L)
FBG $\leq$ 5.3	84	Normal	4.65 $\pm$ 0.05	6.68 $\pm$ 0.27	2.19 $\pm$ 0.031
FBG $>$ 5.3	81	Hyperglycemic	7.13 $\pm$ 0.23*	8.89 $\pm$ 0.39*	2.59 $\pm$ 0.061*
FBG $\leq$ 7.0	141	Normal	5.22 $\pm$ 0.07	7.13 $\pm$ 0.20	2.27 $\pm$ 0.027
FBG $>$ 7.0	24	Hyperglycemic	9.68 $\pm$ 0.46*	11.51 $\pm$ 0.94*	3.08 $\pm$ 0.126*
RBG $\leq$ 7.8	103	Normal	5.26 $\pm$ 0.11	5.80 $\pm$ 0.09	2.19 $\pm$ 0.026
RBG $>$ 7.8	62	Hyperglycemic	6.88 $\pm$ 0.32*	11.03 $\pm$ 0.37*	2.72 $\pm$ 0.072*
RBG $\leq$ 11	141	Normal	5.52 $\pm$ 0.11	6.74 $\pm$ 0.15	2.29 $\pm$ 0.031
RBG $>$ 11	24	Hyperglycemic	7.87 $\pm$ 0.68*	13.79 $\pm$ 0.60*	2.96 $\pm$ 0.128*

Values are mean $\pm$ standard error of means; *P<0.001 versus respective normal group.

DISCUSSION

Our results showed a significant correlation between FBG and RBG levels. The criteria of FBG >7.0 mmol/L resulted 24 subjects to be hyperglycemic (Table 2); of these 24 patients, 3 patients had incompatible RBG (≤ 7.8 mmol/L) and cFruct (≤ 2.5 mmol/L) whereas 2 patients each had incompatible RBG or cFruct levels. Similarly, the use of RBG >11.0 mmol/L assigned 24 subjects with hyperglycemia (Table 2); 6 of them had incompatible FBG (≤ 5.3 mmol/L) and cFruct (≤ 2.5 mmol/L) and 1 each with incompatible FBG or cFruct. Although both the criteria (FBG > 7.0 or RBG >11.0 mmol/L) resulted 24 patients to be hyperglycemic the identity of these patients was not common with each criteria suggesting the poor efficiency of these tests. Although FBG is a simplest and commonly used screening test for GDM (26) its poor performance should not be ignored (27-29). Larsson et al (29) have suggested that a single FBG is not useful for screening of diabetes. They observed that reducing the FBG cut-off value from 6.0 mmol/L to 4.8 mmol/L increased the sensitivity from 53.4% to 85.9% at the expense of poor specificity (45%) (29). Lowering the threshold value of FBG to 4.4 mmol/L did not miss any case of GDM (100% sensitivity) but with very low specificity and a very high percentage (55%) of false-positive results (30). Recently, a FBG threshold of 4.7 mmol/L reached the minimal acceptable sensitivity of 78.1% with a corresponding unacceptable specificity of 32.2% (31). Several investigators have also reported the use of RBG for short-listing patients for OGTT (32,33). However, RBG alone cannot be considered as an efficient screening test for the detection of GDM (6,7). According to Bhattacharya (27), both FBG and RBG alone cannot be regarded as efficient screening tests for GDM, particularly in the later months of pregnancy.

A significant correlation was observed between FBG and cFruct (Fig. 2a) which is in accordance with earlier studies (13,22,23). RBG also showed significant correlation with cFruct (Fig. 2b). Significant correlations between serum fructosamine and preprandial (17) or postprandial (24) blood glucose levels have been reported earlier. Both FBG and RBG reflect the instant blood glucose level without predicting a time-course glycemic history. Whereas, serum fructosamine is a simple, sensitive and precise method for the evaluation of glycemic control within a few weeks time (2-3 weeks) and is therefore more advantageous in timely detection of responses to diabetic treatment plan (11). However, fructosamine assay is associated with poor sensitivity and specificity for diagnostic purpose (34). Bor et al (35) observed that fructosamine alone has low sensitivity as predictor of GDM and therefore cannot be recommended for screening of GDM.

On the other hand, use of paired values of cFruct and FBG or RBG instead of their individual performance could be a sensitive and safe strategy to filter high-risk patients while avoiding OGTTs in the remaining large number of normal cases. The combination of a moderate cut-off value of FBG (> 5.3 mmol/L) with cFruct (> 2.5 mmol/L) identified 35 high risk patients on whom a confirmatory OGTT could be performed (Fig. 2a). However, this strategy was associated with 8 (4.8%) false-positive and 6 (3.6%) false-negative outcomes. On the other hand, combination of RBG > 7.8 mmol/L with cFruct > 2.5 mmol/L filtered 32 high-risk patients with 5 (3.0%) each of false-positive and false-negative predictions (Fig. 2b). The individual performance of these tests for filtering hyperglycemic subjects using the above respective cut-off value was as follows: FBG alone (81 subjects), RBG alone (62 subjects) and cFruct alone (42 subjects). Various cut-off values of both FBG (29,31,36) and serum fructosamine (23,36,37) have been used to maintain a balance between false-positive and false-negative results. Agarwal and Punnoose (25) pointed out that FBG alone can eliminate the need for 57.8% OGTTs by using the cut-off values of FBG ≥ 5.3 mmol/L to rule-in GDM and FBG < 4.4 mmol/L to rule-out GDM. However, if FBG is used in conjunction with cFruct, additional 10.4% patients would not need OGTT (25). It is clear from the above studies that the sensitivity can be increased using high cut-off values but with a corresponding decrease in the specificity.

In conclusion, the paired values of cFruct with FBG or RBG could be utilized in avoiding unnecessary OGTT in a large number of cases as suggested earlier (25,31,36,37). Moreover, since the cFruct is a reliable test for understanding the short-term glycemic history the strategy of paired values can also be utilized for the subsequent monitoring of GDM.

REFERENCES

1. Kendrick JM. Preconception care of women with diabetes. *J Perinat Neonat Nurs* 2004;18:14-25.
2. American Diabetic Association. Standards of medical care in diabetes. *Diab Care* 2004;27 (Suppl 1):S15-S35.
3. Catalano PM, Avallone DA, Drago NM, Amini SB. Reproducibility of the oral glucose tolerance test in pregnant women. *Am J Obstet Gynecol* 1993;169:874-81.
4. Rey E, Hudon L, Michon N, Boucher P, Ethier J, Saint-Louis P. Fasting plasma glucose versus glucose challenge test: screening for gestational diabetes and cost effectiveness. *Clin Biochem* 2004;37:780-4.

5. Lani S, Barrett D. The predictive value of the 1-h 50-g glucose screen for diagnosing gestational diabetes mellitus in a high-risk population. *J Matern Fetal Neonat Med* 2004;15:375-9.
6. Perea-Carrasco R, Perez-Coronel R, Albusac-Aguilar R, Lombardo-grifol M, Bassas-Baena de Leon E, Romero-Diaz C. A simple index for detection of gestational diabetes mellitus. *J R Soc Med* 2002;95:435-9.
7. Miyakoshi K, Tanaka M, Ueno K, Uehara K, Ishimoto H, Yoshimura Y. Cutoff value of 1 h, 50 g glucose challenge test for screening of gestational diabetes mellitus in a Japanese population. *Diab Res Clin Pract* 2003;60:63-7.
8. Laird MD, McFarland MD, Face KF. Fasting blood glucose and initiation of insulin therapy in gestational diabetes. *Endocr Pract* 1996;2:330-2.
9. Hatem M, Dennis KJ. A random plasma glucose method for screening for abnormal glucose tolerance in pregnancy. *Br J Obstet Gynaecol* 1987;94:213-6.
10. Maheshwari JR, Mataliya MV. A random plasma glucose method for screening for gestational diabetes. *J Postgr Med* 1989;35:36-9.
11. Austin GE, Wheaton R, Nanes MS, Rubin J, Mullins RE. Usefulness of fructosamine for monitoring outpatients with diabetes. *Am J Med Sci* 1999;318:316-23.
12. Goldstein DE, Little RR, Wiedmeyer HM, England JD, McKenzie EM. Glycated hemoglobin: methodologies and clinical applications. *Clin Chem* 1986;32:B64-B70.
13. Koskinen P, Irjala K, Viikari J, Panula-Ontto R, Matikainen MT. Serum fructosamine in the assessment of glycaemic control in diabetes mellitus. *Scand J Clin Lab Invest* 1987;47:285-92.
14. Peiris DS. The value of serum fructosamine in comparison with oral glucose tolerance test (OGTT) as a screening test for detection of gestational diabetes mellitus. *J Obstet Gynaecol* 2000;20:136-8.
15. Hughes PF, Agarwal M, Newman P, Morrison J. An evaluation of fructosamine estimation in screening for gestational diabetes mellitus. *Diabet Med* 1995;12:708-12.
16. Parfitt VJ, Clark JD, Turner GM, Hartog M. Use of fructosamine and glycated haemoglobin to verify self blood glucose monitoring data in diabetic pregnancy. *Diab Med* 1993;10:162-6.
17. Frandsen EK, Sabagh T, Bacchus RA. Serum fructosamine in diabetic pregnancy. *Clin Chem* 1988;34:316-9.
18. Roberts AB, Baker JR. Serum fructosamine: a screening test for diabetes in pregnancy. *Am J Obstet Gynecol* 1986;154:1027-30.
19. Roberts AB, Baker JR, James AG, Henley P. Fructosamine in the management of gestational diabetes. *Am J Obstet Gynecol* 1988;159:66-71.
20. Weerasekera DS, Peiris H. The value of serum fructosamine in comparison with oral glucose tolerance test (OGTT) as a screening test for detection of gestational diabetes mellitus. *J Obstet Gynaecol* 2000;20:136-8.
21. Salemans TH, van Dieijen Visser MP, Brombacher PJ. The value of HbA1c and fructosamine in predicting impaired glucose tolerance-an alternative to OGTT to detect diabetes mellitus or gestational diabetes. *Ann Clin Biochem* 1987;24:447-52.
22. Hom FG, Ettinger B, Lin MJ. Comparison of serum fructosamine vs glycohemoglobin as measures of glycemic control in a large diabetic population. *Acta Diabetol* 1998;35:48-51.
23. Mula Abed WA, Al Naemi AH. Performance indicators and validity of serum fructosamine assay as a diagnostic test in a screening program for diabetes mellitus. *Saudi Med J* 2003;24:477-84.
24. Kennedy DM, Johnson AB, Hill PG. A comparison of automated fructosamine and HbA1c methods for monitoring diabetes in pregnancy. *Ann Clin Biochem* 1998;35:283-9.
25. Agarwal MM, Punnose J. Screening for gestational diabetes in high-risk populations: the United Arab Emirates Experience. *Ann Saudi Med* 2001;21:117-9.
26. Laird MD, McFarland MD, Face KF. Fasting blood glucose and initiation of insulin therapy in gestational diabetes. *Endocr Pract* 1996;2:330-2.
27. Bhattacharya SM. Fasting or two-hour postprandial plasma glucose levels in early months of pregnancy as screening tools for gestational diabetes mellitus developing in later months of pregnancy. *J Obstet Gynaecol Res* 2004;30:333-6.
28. Cypriak K, Czupryniak L, Wilczynski J, Lewinski A. Diabetic screening after gestational diabetes mellitus: poor performance of fasting plasma glucose. *Acta Diabetol* 2004;41:5-8.
29. Larsson H, Ahren B, Lindgrade F, Berglund G. Fasting blood glucose in determining the prevalence of diabetes in a large, homogeneous population of Caucasian middle-aged women. *J Intern Med* 1995;237:537-41.
30. Perucchini D, Fischer U, Spinass GA, Huch R, Huch A, Lehmann R. Using fasting plasma glucose concentrations to screen for gestational diabetes mellitus: prospective population based study. *Br Med J* 1999;319:812-5.
31. Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes in a high-risk population: using the fasting plasma glucose to simplify the diagnostic algorithm. *Eur J Obstet Gynecol Reprod Biol* 2005;120:39-44.
32. Nasrat AA, Johnstone FD, Hasan SA. Is random plasma glucose an efficient screening test for abnormal glucose tolerance in pregnancy? *Br J Obstet Gynaecol* 1988;95:855-60.

33. Nielsen IK, Vinther S, Birch K, Lange AP. Random blood glucose sampling as an early antenatal screening test for diabetes mellitus. *Diab Res* 1988;8:31-3.
34. Baker JR, O'Connor JP, Metcalf PA, Lawson MR, Johnson RN. Clinical usefulness of estimation of fructosamine concentration as a screening test for diabetes mellitus. *Br Med J* 1983;287:863-7.
35. Bor MV, Bor P, Cevik C. Serum fructosamine and fructosamine-albumin ratio as screening tests for gestational diabetes mellitus. *Arch Gynecol Obstet* 1999;262:105-11.
36. Ko GTC, Chan JCN, Yeung VTF, et al. Combined use of fasting plasma glucose concentrations and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects. *Diab Care* 1998;21:1221-5.
37. Agarwal MM, Hughes PF, Punnose J, Ezimokhai M, Thomas L. Gestational diabetes screening of a multiethnic, high-risk population using glycated proteins. *Diab Res Clin Pract* 2001;51:67-73.