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Reliability of glycosylated hemoglobin in the diagnosis of gestational diabetes mellitus

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Abstract

Background: Oral glucose tolerance test (OGTT) performed at 24-28 weeks gestation is the current recommended method to the diagnosis of gestational diabetes mellitus (GDM). Many recent studies investigating HbA1c in detecting GDM yield different results. There are no published data on HbA1c in the diagnosis of GDM in Sub-Saharan countries including Sudan.

Methods: A cross-sectional study was carried out at the antenatal care of Saad Abuelela Maternity Hospital, Khartoum, Sudan during the period from February to November 2018 to assess the reliability of HbA1c in the diagnosis of GDM. GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Groups using a 75-g oral glucose tolerance test.

Results: Three hundred and forty-eight women were enrolled. The mean (SD) of the age, gravidity, and gestational age of the enrolled women were 27.8 (5.6) years, 2.36 (2.2) and 26.26 (2.43) weeks, respectively. Sixty-eight women (19.5%) had GDM. A poor productively for HbA1c in diagnosis GDM was shown (AUC = 0.62, 95% CI = 0.55-0.69). At HbA1c level of 4.150%, the sensitivity and specificity of the diagnosis for GDM were 76.51% and 37.85%, respectively. At HbA1c level of 5.850%, the sensitivity and specificity of the diagnosis for GDM were 13.24% and 91.43%, respectively. While there was no significant (Spearman) correlation between fasting blood glucose and HbA1c, there were significant correlations between HbA1c and OGTT 1 and 2 hours of OGTT.

Conclusion: In this study, HbA1c has a poor reliability, insufficient sensitivity or specificity for use to diagnose GDM.

KEYWORDS
gestational diabetes, glucose tolerance test, hemoglobin A1c, pregnancy, Sudan

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is defined when glucose intolerance resulting in different severity level of hyperglycemia is discovered during gestation/pregnancy.[1] GDM is one of the common public health problems worldwide, and its prevalence is expected to increase dramatically.[2,3] GDM is one of the leading causes of adverse maternal and fetal outcomes such as hypertensive disorders of pregnancy, increased cesarean delivery rate, fetal overgrowth,[4] type 2 diabetes, cardiovascular diseases in later life in mothers, and increased risk for macrosomia.[5]

Oral glucose tolerance test (OGTT) performed at 24-28 weeks of gestation is the current recommended test to diagnose GDM. However, it necessitates fasting for 10 hours, waiting for at least two hours, require labor and repeated venipunctures. HA1c is the measurement of glycated hemoglobin which is used routinely as an indicator of blood glucose control in the prior 3 months. It may be the way for earlier identification of women at risk of GDM. Currently, international guidelines "(American Diabetic Association and the International Expert Committee on Diabetes)" recommend the use of HA1c for the diagnosis of diabetes rather than the measurement of fasting or postprandial plasma glucose in non-pregnant population.[6] Moreover, HbA1c measurement if it is performed in early pregnancy could be of value in diagnosing preexisting diabetes.[7-9] A number of studies have demonstrated elevated levels of HbA1c in women with GDM.[10-14] Moreover, elevated levels of HbA1c during pregnancy were associated with adverse neonatal outcome.[4,15] Recent studies have reported various levels of reliability/accuracy of HbA1c in diagnosing GDM. While some studies have shown a poor reliability,[10,16-18] others have shown a good or excellent reliability of HbA1c in diagnosing GDM.[12,14,19-21]

There was a paucity of published data on HbA1c for the diagnosis of GDM in Sub-Saharan Africa. A recent meta-analysis has shown a high prevalence of GDM in Africa[22]; hence, there is a need to assess HbA1c for the diagnosis of GDM. The aim of the current study was to determine the reliability/accuracy of HbA1c for the diagnosis of GDM among Sudanese women.

2 | METHODS

A cross-sectional study was carried out at the antenatal care of Saad Abuelela Maternity Hospital, Khartoum, Sudan during the period from February to November 2018. After signing an informed consent form, sequential pregnant Sudanese women with singleton pregnancy, who were ≥18 years old, have been in good health (not suffering from any disease), attended the antenatal clinic (between 24 and 28 weeks of gestational age) and consuming a normal diet (without any restriction) were enrolled in this study. Smoker, women with chronic diseases such as severe anemia (hemoglobin < 7 g/dL), hypertension, type 1 or type 2 diabetes, renal disease, thyroid disease and liver disease, or taking chronic medication were excluded. The details of the age, parity, gestational age, education, residence, history of diabetes, history of miscarriage, and history of intrauterine fetal death were collected using a questionnaire. Then women's weight and height were recorded and were used to compute body mass index (BMI) as weight in kg/(height in m)^2. A 75-gram oral glucose tolerance test was performed following overnight fasting (for 10 hours). Two mL sample was collected in fluoride vacutainer in fasting state followed by 75 g oral glucose load and 1 and 2 hours postprandial samples. A sample of 2 mL of blood was collected in ethylenediaminetetraacetic acid vacutainer for assessment of glycosylated hemoglobin. The diagnosis of GDM in this study was based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations "fasting blood glucose (FBG) ≥ 92 mg/dL or 1-hour blood glucose ≥ 180 mg/dL and/or 2-hour blood glucose ≥ 153 mg/dL, after 75-g oral glucose load".[23] Glucose oxidase method was used to measure glucose level following the manufacturer's instructions (Shino-Test Corp.). An Ichroma machine (Republic of Korea) was used to measure HbA1c levels.

The sample size of 348 women was calculated to obtain the desired sensitivity (90%), and specificity (70%) for the prevalence (15%) of GDM among the screened women. This sample would provide 80% power to detect type I error (ie, P-value < .05), with the assumption that complete data or enough samples might not be available for 10% of the women.[24]

2.1 | Statistics

Data were entered in a computer using SPSS (version 20) for Windows for data analysis. Normality of distribution of continuous data was assessed, and mean (standard deviation) or median (interquartile) was used to express the normally distributed and abnormally distributed variables, respectively. t Test and non-parametric test (Mann-Whiney U) were used to compare normally distributed and abnormally distributed data between the women with GDM and women with no GDM, respectively. A X^2 test was used to compare the proportions between the two groups. Reliability tests (sensitivity, specificity) and cutoff values for HbA1c were performed by the receiver operating characteristic (ROC) curve and the area under the curve (AUC).[25] The agreement between HbA1c levels and the values of the GTT (1 and 2 hours) were assessed using Bland-Altman plot. Spearman correlations between OGTT and HbA1c were performed. A two sided. A P-value < .05 was considered statistically significant.

2.2 | Ethics

This study was approved by the Research Ethical Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Khartoum, Sudan (#2018, 08).

3 | RESULTS

The mean (SD) age, gravidity, and gestational age of the enrolled women (348) were 27.8 (5.6) years, 2.36 (2.2), and 26.26 (2.43)

TABLE 1 Sensitivity and specificity for all values of HbA1c

Hemoglobin A1c	Sensitivity %	95% CI	Specificity %	95% CI	Likelihood ratio
2.150	100	94.72%-100.0%	1.786	0.5823%-4.118%	1.018
2.350	100	94.72%-100.0%	2.143	0.7904%-4.605%	1.022
2.450	100.00	94.72%-100.0%	2.857	1.241%-5.552%	1.029
2.600	100.0	94.72%-100.0%	4.286	2.234%-7.367%	1.045
2.750	98.53	92.08%-99.96%	6.071	3.576%-9.543%	1.049
2.850	97.06	89.78%-99.64%	10.36	7.047%-14.54%	1.083
2.950	95.59	87.64%-99.08%	12.14	8.558%-16.55%	1.088
3.050	94.12	85.62%-98.37%	15.36	11.34%-20.12%	1.112
3.150	94.12	85.62%-98.37%	16.43	12.29%-21.30%	1.126
3.250	92.65	83.67%-97.57%	20.36	15.80%-25.56%	1.163
3.350	92.65	83.67%-97.57%	21.43	16.77%-26.70%	1.179
3.450	92.65	83.67%-97.57%	22.14	17.42%-27.47%	1.19
3.550	92.65	83.67%-97.57%	26.43	21.36%-32.00%	1.259
3.650	91.18	81.78%-96.69%	27.14	22.02%-32.75%	1.251
3.750	91.18	81.78%-96.69%	28.21	23.02%-33.88%	1.27
3.850	86.76	76.36%-93.77%	29.29	24.02%-34.99%	1.227
3.950	85.29	74.61%-92.72%	31.43	26.03%-37.22%	1.244
4.050	77.94	66.24%-87.10%	34.29	28.74%-40.17%	1.186
4.150	76.47	64.62%-85.91%	37.86	32.15%-43.82%	1.231
4.250	73.53	61.43%-83.50%	40.00	34.22%-46.00%	1.225
4.350	70.59	58.29%-81.02%	42.14	36.29%-48.16%	1.22
4.450	69.12	56.74%-79.76%	44.64	38.73%-50.67%	1.249
4.510	64.71	52.17%-75.92%	47.5	41.53%-53.53%	1.232
4.560	63.24	50.67%-74.61%	48.93	42.93%-54.95%	1.238
4.650	63.24	50.67%-74.61%	54.29	48.25%-60.23%	1.383
4.750	60.29	47.70%-71.96%	59.64	53.64%-65.44%	1.494
4.850	50.00	37.62%-62.38%	62.86	56.91%-68.53%	1.346
4.950	47.06	34.83%-59.55%	67.5	61.67%-72.95%	1.448
5.050	45.59	33.45%-58.12%	70.71	65.01%-75.98%	1.557
5.150	42.65	30.72%-55.23%	76.43	71.01%-81.28%	1.809
5.250	36.76	25.39%-49.33%	80.00	74.83%-84.52%	1.838
5.350	35.29	24.08%-47.83%	83.57	78.70%-87.71%	2.148
5.450	32.35	21.51%-44.79%	85.71	81.06%-89.59%	2.265
5.550	26.47	16.50%-38.57%	86.79	82.25%-90.52%	2.003
5.650	20.59	11.74%-32.12%	88.21	83.85%-91.75%	1.747
5.750	17.65	9.465%-28.80%	90.00	85.87%-93.25%	1.765
5.850	13.24	6.235%-23.64%	91.43	87.52%-94.43%	1.544
5.950	11.76	5.218%-21.87%	93.57	90.03%-96.15%	1.83
6.050	10.29	4.240%-20.07%	93.93	90.46%-96.42%	1.696

weeks, respectively. Fifty-two (14.9%) of 348 women were rural residents, 101(29.02) were housewives, and 41(11.78%) women had an education level less or equal to secondary level. Eighty (22.98%) and 180 (51.72) women had a history of miscarriage and had a family history of diabetes mellitus, respectively. The mean (SD) hemoglobin level was 11.2 (0.9) g/dL, and 95 (27.3%) women were anemic (hemoglobin < 11.0 g/dL).

The median (interquartile) range of BMI was 26.92 (24.41-30.80) kg/m^2. The median (interquartile) range of fasting blood glucose, I hour OGTT, 2 hours OGTT, and Hb A1c were 70.0 (63.0-77.0) mg/

dL, 133.0 (114.0-153.0) mg/dL, 118.0 (100.0-139.0) mg/dL, and 4.6 (3.8-5.2) %, respectively.

Sixty-eight women (19.5%) had GDM as defined above. The median (interquartile) range of fasting blood glucose [75.5 (68.0-91.0) mg/dL vs 68.0 (62.0-76.0) mg/dL, $P < .001$], I– hour OGTT [163.0 (145.2-179.5) mg/dL vs 126.0 (111.0-142.7) mg/dL, $P < .001$], 2-hours OGTT [162.0 (153.2-176.7) mg/dL vs 111.0 (96.2-128.7) mg/dL, $P < .001$] and HbA1c [4.8 (4.2-5.6)% vs 4.6 (3.5-5.1)%, $P = .001$] were significantly higher in women with GDM.

Receiver operating characteristic curve analysis and calculation of the AUC for HbA1c were performed for prediction of GDM. A poor GDM productively for HbA1c was shown (AUC = 0.62, 95% CI = 0.55-0.69), $P = .001$). At HbA1c level of 4.150%, the sensitivity, specificity, positive predictive value, and negative predictive value were 76.51%, 37.85%, 23.0%, and 86.90%, respectively, in the diagnosis for GDM. At HbA1c level of 5.850%, the sensitivity, specificity positive predictive value, and negative predictive were 13.24%, 91.43%, 27.2%, and 81.32%, respectively, Table 1, Figure 1.

While there was no significant (Spearman) correlation between fasting blood glucose and HbA1c, there were significant correlations between HbA1c and OGTT 1 and 2 hours of OGTT. Likewise, while

FIGURE 1 ROC curve analysis and calculation of the AUC for HbA1c

there was no significant correlation between fasting blood glucose and hemoglobin, there were significant correlations between hemoglobin and OGTT 1 and 2 hours of OGTT. There was no correlation between hemoglobin and HbA1, Table 2.

Bland-Altman correlations between OGTT and HbA1c are shown in Figures 2 and 3. The HbA1c distribution by GDM status is shown in Figure 4.

4 | DISCUSSION

In the current study, the median HbA1c level was significantly higher in women with GDM compared with women who had no GDM (4.8% vs 4.6%, $P = .001$). These findings are in agreement with the previous studies which reported a significantly higher HbA1c values in women with GDM compared with HbA1c values in women without GDM.[10-14]

The current study has shown a poor reliability of HbA1c for the diagnosis of GDM (AUC = 0.62). This finding was similar to the previous studies findings [10,16-19] which reported that HbA1c values cannot replace OGTT for the diagnosis of GDM. On the other hand, several previous studies have shown a high efficiency with a good/excellent reliability of HbA1c for the diagnosis of GDM in which the AUC values ranged from 0.805 to 0.937.[12,14,21] Interestingly, in a recent meta-analysis enrolling 6406 pregnant women in eight studies, a good level of diagnostic accuracy (AUC = 0.825) of HbA1c for the diagnosis of GDM has been reported.[20]

In our study, at HbA1c level of 5.850% the sensitivity and specificity for the diagnosis of GDM was 13.24% and 91.43%, respectively. Recently, Patcharaporn et al[13] have reported a 17.1% and 100.0% sensitivity and specificity, respectively, for HbA1c for the diagnosis of GDM at 5.8% cutoff point. A 26.4% sensitivity and 94.9% specificity were reported when HbA1c of 5.8% was used as a cutoff point.[20] A previous study suggested the use of HbA1c at 5.95% as a cutoff point to confirm the diagnosis of GDM in women in India (28.6% and 97.2% for sensitivity and specificity, respectively).[26]

TABLE 2 Spearman correlations between OGTT, HbA1c, and hemoglobin
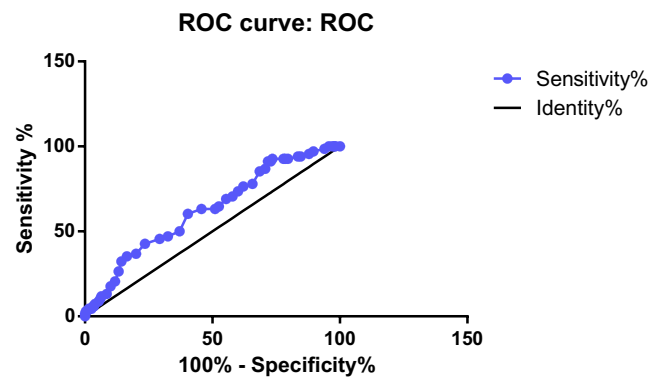
Variable	Fasting blood glucose	OGTT 1 h, mg/dL	OGTT 2 h, md/dL	HBA1C%	Hemoglobin, gm/dL
	r	r	r	r	r
	P	P	P	P	P
Fasting blood glucose		.318	.265	.101	.06
		<.001	<.001	.060	.397
OGTT 1 h, mg/dL			.703	.168	.198
			<.001	.002	<.001
OGTT 2 h, md/dL				.230	.148
				<.001	.006
HBA1C%					−.030
					.579

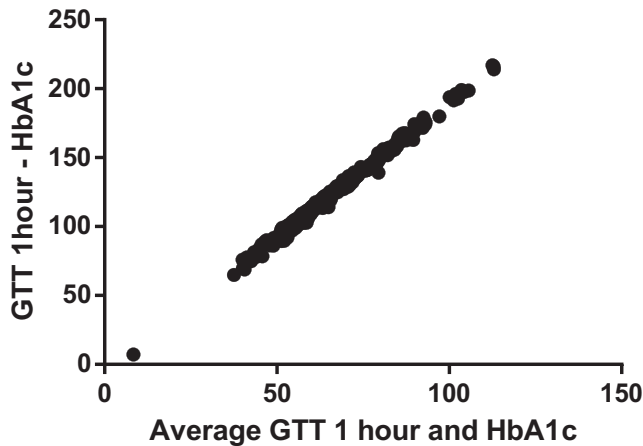Abbreviations: HbA1c, glycosylated hemoglobin; OGTT, oral glucose tolerance test.

FIGURE 2 Bland-Altman correlations between oral glucose tolerance test 1 h and HbA1c
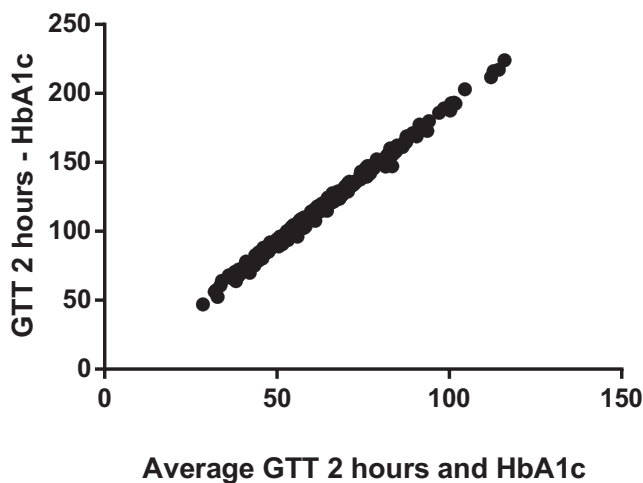

FIGURE 3 Bland-Altman correlations between oral glucose tolerance test 2 h and HbA1c
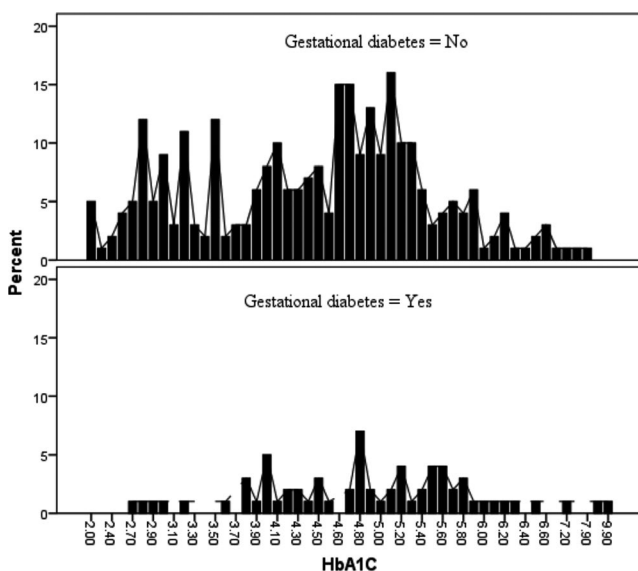

FIGURE 4 HbA1c distributions by gestational diabetes mellitus status

Recently, Dubey et al[14] have shown that by using a WHO 75 g OGTT criteria for the diagnosis of GDM, HbA1c at a cutoff ≥ 5.45% has the higher sensitivity (84.3%) and specificity (81.8%). Various levels of sensitivity and specificity (50.3% and 83.7%; 24.7% and 95.5% for the cutoffs of 5.4% and 5.7%, respectively) of HbA1 for the diagnosis GDM have been reported in the recent meta-analysis.[20] It is worth mentioning that HbA1c level might have different and varied values according to the gestational age.[27-29]

In the current study, while there was no correlation of HbA1c and fasting blood, significant positive correlations were found between of HbA1c with 1 and 2 hours. A previous study has reported significant correlations of HbA1c with fasting blood and 2 hours postprandial blood glucose.[14]

Our results and the results of the later studies should be compared cautiously because different studies used different diagnostic criteria for GDM.[30,31] Moreover, the high rate of anemia (27.3%) in our study might explain the poor reliability of HbA1c for the diagnosis of the GDM. O'Connor et al[26] have suggested that anemia was one of the explanations for the lower HbA1c levels among pregnant women. HbA1c reference ranges may vary according to gestational age, ethnicity, genetic difference, and exposure to different risk factors.[32-34] It is worth mentioning that HbA1c assay during pregnancy was recently reported to be not cost effective as a screening method for GDM.[35]

5 | CONCLUSION

In this study, HbA1c has a poor reliability, insufficient sensitivity, and specificity to diagnose GDM.

5.1 | Limitation of the study

Various other factors that could have effects on the HbA1c and GDM such as or ferritin, iron levels, and hepcidin were not assessed in our study.[36,37] We failed to follow-up these women so as to access the maternal and perinatal outcomes in relation to HbA1c.

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