Original Article

Glycated hemoglobin (HbA1c) in diagnosis of gestational diabetes mellitus

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of glycated hemoglobin for diagnosing gestational diabetes mellitus.

Material and Methods: This cross-sectional comparative study was conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology (National University of Medical Sciences), Rawalpindi Pakistan from June 2023 to October 2023. The study included women having gestational amenorrhea between 24th to 28th weeks, who gave informed written consent for a 75-gram oral glucose tolerance test (OGTT) at AFIP, Rawalpindi. Women with diabetes, hypertension, hemoglobin< 10g/dl, on steroid treatment, with gastrointestinal or thyroid diseases were excluded. The medical history and anthropometric measurement (height, weight, body mass index (BMI) and blood pressure were recorded on a predesigned proforma. Blood sample for glucose was taken in sodium fluoride tubes and HbA1c in potassium EDTA tubes. American Diabetes Association criteria 2023 was used to diagnose gestational diabetes mellitus (GDM). Study participants were divided into two groups on basis of 75g- OGTT results; Group 1 included GDM and Group 2 Normal Glucose Tolerance (NGT).

Results: A total of 100 pregnant ladies were enrolled whose ages ranged from 15-45 (mean & SD 29±5 & 31±6 years in groups 1& 2 respectively). Mean fasting plasma glucose (FPG) was 5.11±0.6 mmol/l & 4.57±0.4mmol/l, and HbA1c was 6.12%±1 & 5.26% ±0.48 in groups 1& 2 respectively. GDM was found in 19 (group 1) of 100 patients, while 81 responded normally. HbA1c at 5.6% has 84.2% sensitivity, 87.6% specificity, 61.5% PPV, 95.9% NPV and 87% diagnostic accuracy. FPG, 1hr glucose and HbA1c exhibited an Area Under Curve (AUC) by Receiver Operating Characteristic (ROC) Curve of 0.762, 0.801 and 0.894 respectively.

Conclusion: HbA1c has shown higher diagnostic yield for gestational diabetes mellitus and can be used as a screening test.

Keywords: Glycated hemoglobin, Oral glucose tolerance test, Gestational diabetes mellitus

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a complicated condition that poses significant health risks to both mothers and neonates, characterized by elevated blood glucose levels during pregnancy. The Incidence of GDM is increasing in parallel to improvements in life standards and health awareness. The estimated global prevalence has been reported to be 14% by International Diabetes Federation and reported prevalence in Pakistan is 9.47% [1,2].

GDM presents unique challenges to heath care providers, as it typically arises during pregnancy and often settles postpartum, however it carries prolonged health implications for mothers and their babies. Maternal complications may include an increased risk of developing Type 2 Diabetes Mellitus (T2DM) post-partum [3], while babies have an increased risk of neonatal hypoglycemia, macrosomia and an increased vulnerability to obesity and T2DM during their own lifetimes. GDM, if not managed, can lead to adverse pregnancy consequences, such as pre-eclampsia and preterm birth [4].

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Accurate and timely diagnosis of GDM is vital to alleviate these risks and guarantee the best possible outcome to both mothers and infants. Traditionally, GDM diagnosis has relied mostly on the OGTT, a diagnostic test requiring fasting and multiple blood glucose measurements [5]. This method, while effective, has limitations, including patient inconvenience, potential false-positive results, and variable international diagnostic criteria. Similarly, there is requirement for a minimum 8 hours medical fast, 3 blood samples, risk of vomiting, and increased chances of variability. Similarly, over 10% of pregnant women fail to finish the OGTT process [6]. Despite these challenges, OGTT remains an important diagnostic tool for GDM due to its ability to identify pregnancies with unfavorable outcomes. International associations have made efforts to standardize diagnostic criteria, such as those proposed by the ADA, to improve the accuracy and consistency of GDM diagnosis [7].

HbA1c, on the other hand, is a widely used biomarker in the management of diabetes, reflecting average plasma glucose over the preceding 2-3 months [8]. Its application in diagnosing GDM is a topic of growing interest and research [9,10]. Latest research indicates that HbA1c may serve as a useful screening tool for GDM, although it should not be relied upon as a complete substitute for OGTT [11]. Retnakaran *et al* have indicated that assessing HbA1c levels before pregnancy, on average 1.4 years earlier, strongly predicted GDM. Each 0.1% rise in pregravid HbA1c raised the risk of GDM in a next pregnancy by 22% [12]. Similarly diagnostic role of HbA1c in GDM has been proved by different researchers [13,14]. However, Liu X *et al* have emphasized that further research and clinical practice support are still needed for the application of HbA1c in GDM [15]. Furthermore, there were constant Hba1c variations throughout pregnancy between women diagnosed with GDM and control group [16]. Other studies have reached similar conclusions, stating that HbA1c levels, which are used to diagnose pre-diabetes in non-pregnant individuals, are also linked to the development of GDM. These findings support the use of HbA1c as a tool for predicting GDM [17].

Keeping in view the prevalence of GDM in our country, its dreadful effects and usefulness of timely diagnosis, present study was planned to evaluate the diagnostic performance of HbA1c among the females at risk of GDM.

MATERIAL AND METHODS

The cross-sectional study was conducted in the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi from June 2023 to October 2023 after approval from the Institutional Review Board reference number: Cons-CHP-3/READ-IRB/23/2219.

Sample size calculation was performed using the World Health Organization sample size calculator, which came out to be 100, keeping in view the prevalence of GDM at 9.47% in Pakistan [2]. Pregnant ladies between 18-45 years of age, having gestational amenorrhea between 24th to 28th weeks who were referred to AFIP for 75g OGTT were enrolled in the study after obtaining informed written consent. Known diabetics, hypertensives, gastrointestinal and thyroid disorders were excluded. Ladies with Hemoglobin <11 g/dl or taking hematinics were also excluded. History and measurements of anthropometric indices like height, weight, BMI & blood pressure were recorded. Blood samples were taken in sodium fluoride and Potassium EDTA tubes for blood glucose and HbA1c, respectively.

Plasma glucose analysis was performed using the Hexokinase Method and HbA1c by Turbidimetric inhibition immunoassay (TINIA) on the Cobas Pure by Roche Diagnostics, (a fully automated Chemistry Analyzer). The diagnosis of GDM was confirmed using the diagnostic criteria established by the ADA 2023 [18]. Based on the findings, participants were categorized into two groups: Group 1 with GDM, and Group 2 with NGT.

The data analysis was conducted using the Statistical Package for Social Sciences (SPSS) program version 25.0. Data distribution was tested by Shapiro-Wilk test and found to be normally distributed. The results were reported as the mean ± standard deviation (SD). An independent t-test was utilized to compare the HbA1c and OGTT results. The Area under the curve for FPG, 1-hour post-OGTT, 2-hour post-OGTT, and HbA1c were compared using ROC curve analysis.

RESULTS

Participants were between 18-45 years of age (mean & SD 29±5 & 31±6 years in groups 1 & 2, respectively). Of the 100 individuals, GDM was found in 19 cases (group 1) and HbA1c was also raised (> 5.6%) in 16 cases in this group, whereas 81 cases showed normal responses. Biochemical results showed mean FPG 5.11±0.66 and 4.57±0.4 mmol/l, HbA1c was 6.12 ±1 and 5.26±0.48 % in groups 1 and 2 respectively.

Results revealed that OGTT had a good association with a previous history of miscarriage/ GDM and significant difference was found among the group's participants who had a history of GDM in previous pregnancies, as depicted in Table-I.

Comparison of the age, BMI, gestational amenorrhea between the GDM and non GDM groups showed no significant difference. The fasting, 1hr, 2 hr. glucose and HbA1c among the groups had statistically significant differences as shown in Table-II.

The diagnostic yield of HbA1c was evaluated using OGTT as a gold standard method for the diagnosis of GDM. Table-III shows the comparison of HbA1c with OGGT as a positive response HbA1c at 5.6% has shown sensitivity, specificity, PPV, NPV& Diagnostic efficacy of 84.2%,87.6%, 61.5%, 95.9% and 87% respectively.

In addition, we conducted ROC curve analysis to compare the AUC values of FPG, 1-hour post OGTT result, 2-hour post-OGTT result, and HbA1c by taking ADA 2023 diagnostic criteria as gold standard.

In ROC curve analysis, the BMI variable demonstrated a moderate discriminatory capacity, as reflected by an AUC value of 0.617 (Figure-I. This suggests that BMI alone may not reliably discern between positive and negative cases. Conversely, FPG variable exhibited a robust discriminatory capacity, with an AUC of 0.762, indicating its strong ability to differentiate GDM. Furthermore, the 1hr glucose outperformed the others, boasting an AUC of 0.801, signifying excellent discriminatory power in identifying GDM. HbA1c has shown exceptional discriminatory performance, with an AUC of 0.894. This means high accuracy of HbA1c at 5.6% to distinguish between positive and negative cases, establishing it as a powerful diagnostic parameter in workup of GDM.

Table-I: Association of OGTT with history of miscarriages and GDM in previous pregnancies (n=100).

		OGTT – Normal Response Count (%)	OGTT – GDM Count (%)	Sig
Miscarriage History	No	32 (82.1%)	7 (17.9%)	0.046
	Yes	49 (80.3%)	12 (19.7%)	
GDM History	Yes	(4.2%)	8(57.1%)	>0.05
	No	69 (95.8%)	6 (42.9%)	

Table-II: Independent samples t-Test between GDM and Non-GDM group (n=100).

Variable	Mean ± SD		p-value
	Normal Response (n= 81)	GDM (n= 19)	
Age (years)	28.94 ±5.023	30.68± 0.51881	.442
Gestational Amenorrhea (weeks)	25.41± 4.623	26.68± 5.100	.601
BMI (kg/m^2)	25.4432 ±3.6124	27.1947±5.010	.170
Fasting Glucose (mmo/l)	4.57±0.40	5.11± 0.66	0.017
Glucose_1hr (mmo/l)	7.24±1.20	9.08±1.67	0.018
Glucose_2hr (mmo/l)	5.95±1.01	7.85±1.77	0.002
HbA1c (%)	5.26±0.48	6.12±1.01	0.001

Table-III: Relationship of GDM with HbA1c at cut-off 5.6% (n=100).

		OGTT	
		Positive 19 (GDM)	**Negative 81 (No GDM)**
HbA1c	Positive (n=26)	16 (TP)	FP (10)
	Negative (n=74)	3 (FN)	TN (71)
Diagnostic Yield			
Sensitivity		TP/TP+FN	84.2%
Specificity		TN/TN+FP	87.6%
PPV		TP/ TP+FP	61.5%
NPV		TN/TN+FN	95.9%
Diagnostic Efficacy		TN +TP/TN+TP+FN+FP	87%

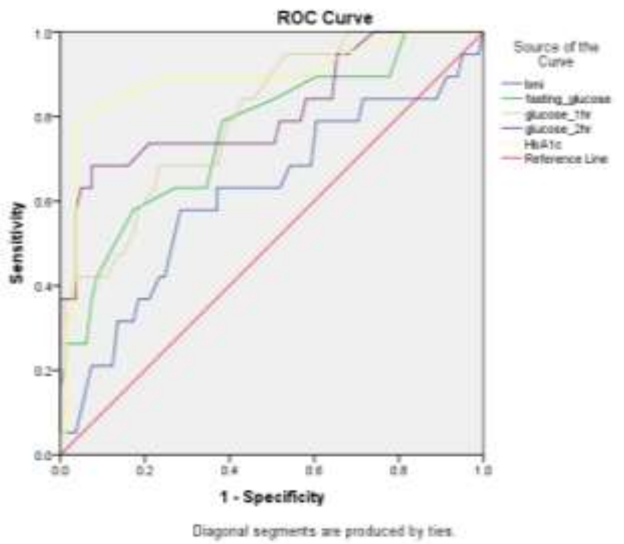

Figure-I: ROC curve analysis of BMI kg/m^2, glucose (fasting, 1hr, 2hr mmol/l) and HbA1c%.

DISCUSSION

Diagnosis of GDM remains a challenge and imperative to save mothers and babies. Among the various methods for assessing glucose metabolism in pregnant women present study has focused on the comparison of HbA1c and OGTT as diagnostic tools.

In present study (n=100) GDM was found in 19 cases, out of which 16 cases also had raised HbA1c (> 5.6%). Results of present study are in accordance with Valdan *et al* (n=700) who found 115 (16.4%) ladies had GDM. The sensitivity, specificity, NPV and PPV for ruling out GDM at even lower HbA1c of 4.85% was 92.2%,32.8%, 95.5% & 21.2% respectively. In addition, at HbA1c cut-off value of 5.45% sensitivity, specificity, NPV and PPV for ruling out GDM was 54.8%, 96.8%, 91.5% and 76.8% respectively. ROC analysis revealed HbA1c to be the most precise parameter for diagnosis, followed by glucose at the 2-hour. Fasting glucose and glucose after 1 hour, both showed good, refined ability. Whereas BMI performed less in this scenario, which is in accordance with present study.

Similarly, Khan SH *et al* discovered that those who showed a delayed peak in their blood glucose levels in OGTT had the highest levels of HbA1c. The highest AUC for the diagnosis of GDM was exhibited by the cumulative sum of all glucose readings. They determined that modifying HbA1c levels can support in decreasing the requirements of OGTT thus advocating use of HbA1c [19].

Similarly Bozkurt L *et al* have reported HbA1c at ≥5.7% during early pregnancies showed higher FPG (90.4±13.2 vs 79.7±7.2 mg/dL, p<0.001), mean plasma glucose (145 ±31 vs 116.2±21.4 mg/dL, as well as highest glucose and tended to a delay in reaching the extreme plasma glucose values in contrast to normal HbA1c, which is also in agreement with present study with mean FPG 4.57±0.4mmol/l and 5.11 mmol/l, HbA1c 5.26% 4±0.48 and 6.12 %±1 in group 1 & 2 respectively [20].

Similarly, Osmundson *et al* (n=2812) found that the risk of GDM was 50% higher in females with a first trimester HbA1c level between 5.7 to 6.4% compared to females with a normal HbA1c level, which also supports present study [21].

Negrea MC *et al* (n=312) studied HbA1c analysis in addition to OGTT in workup of GDM, and found 149 women had GDM. The area under the ROC curve for GDM detection by HbA1c was 0.73 (95% CI 0.68-0.79, p < 0.0001) at cutoff value of HbA1c of 5.5%. The sensitivity, specificity, PPV and NPV for this cutoff were 12.0%, 99.4%, 20 and 0.88, respectively, which supports present study [22].

Another researcher Singh V *et al* (n=200) have found that women who developed GDM had a substantially higher HbA1c level (5.4 ± 0.4%) compared to those who did not develop GDM (4.9 ± 0.2%). In the ROC analysis of HbA1c values for predicting the development of GDM, a threshold value of HbA1c ≥5.25% had 84.8% sensitivity and 62.7% specificity, irrespective of the individual's risk status. Similarly, within the high-risk group, a threshold value of HbA1c ≥5.15% had a sensitivity and specificity of 83.3% & 97% respectively to predict GDM. They concluded that HbA1c could be considered as a potential biomarker for predicting GDM, whose results are also comparable to present study where we used a cutoff of 5.6% in accordance with most of international studies [23].

However, Siricharoenthai P *et al* (n=114) have found The AUC for HbA1c detection of GDM was 0.725 (95% confidence interval 0.621-0.829) at Cut-off value of HbA1c 5.8%. Sensitivity, specificity, PPV, NPV, and accuracy were 17.1%, 100%, 100%, 73.2%, and 74.6%, respectively. They concluded that HbA1c could not replace OGTT for the diagnosis of GDM. However, HbA1c might be a useful tool to reduce the number of OGTT, associated costs and patient inconvenience [24]. Similarly, Yi Lai *et al* (n=19261) found of 3,547 (18.42%) women were diagnosed with GDM. HbA1c was positively, but only weakly correlated with FPG, 1-hour glucose, and 2-hour glucose (r=0.31, 0.24, and 0.25, respectively, P<0.001). The AUC of the HbA1c level for detecting GDM was 0.664 (95% CI: 0.653-0.674, P<0.01) at 5.0%, which yielded a sensitivity, specificity, PPV, and NPV of 60.1%,65.3%, 28.1%, 87.9% respectively, which are different from present study [25].

Participants in present study were between 15-45 years of age (mean & SD 29±5 & 31±6 years in group 1&2 respectively) which is in accordance with earlier studies [11,12,19,21].

LIMITATIONS OF STUDY

It was a single center study which may be influenced by potential confounding variables, such as dietary habits, physical activity, and family history.

CONCLUSION

HBA1C has shown reliable performance in workup of gestational diabetes mellitus and can be used as a screening test.

RECOMMENDATIONS

Longitudinal multicenter studies are required to provide a precise understanding of the relationship between HbA1c and GDM. Additionally, assessing insulin resistance, a hallmark of GDM and T2DM, can provide valuable insights into the condition's pathophysiology and diagnosis.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Muhammad Younas: Idea conception, Write up, literature review, sample collection and analysis

Asif Ali: Literature, data interpretations, critical review

Muhammad Qaiser Alam Khan: Overall supervision and approval of the study

Sajida Shaheen: Proof reading, literature review, revision of the study

Arooj Ishtiaq and Maimoona Roghani: Data collection and statistical review

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