

Original Article

The relationship between glycated hemoglobin and blood glucose levels of 75 and 100 gram oral glucose tolerance test during gestational diabetes diagnosis

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Abstract: Objective: The diagnosis of gestational diabetes mellitus (GDM) is an important issue in terms of prevention of maternal and fetal complications. In our study we aimed to evaluate the relation of HbA1c and blood glucose levels of 75 and 50-100 gram oral glucose tolerance test (OGTT) in pregnant patients who were screened for GDM. Materials and methods: The parameters of 913 pregnant women screened for GDM are evaluated retrospectively. The two steps screening with 50-100 gram OGTT were used in 576 patients. The remaining 337 patients were screened with 75 gram OGTT. Results: The HbA1c levels of patients having high blood glucose (≥ 153 mg/dl) levels at 2nd hour in 75 gram OGTT were significantly higher than patients having normal blood glucose levels at 2nd hour of 75 gram OGTT ($P=0.038$). Correlation analyses showed no significant relation between any blood glucose level of 100 gram OGTT and HbA1c level. Whereas in 75 gram OGTT 1st and 2nd hour blood glucose levels were found to have a significant relation with A1c levels ($P=0.001$, $P=0.001$ respectively). Conclusion: HbA1c may be used as an important tool in the diagnosis of GDM. But due to the variation of HbA1c in pregnant women and there is not an absolute cut-off level for A1c, it may be more reliable to evaluate HbA1c level together with the blood glucose levels in OGTT.

Keywords: Gestational diabetes mellitus, postload glucose, A1c

Introduction

The diagnosis of gestational diabetes mellitus (GDM) is an important issue in terms of prevention of maternal and fetal complications such as preeclampsia, macrosomia, caesarean delivery and their associated morbidities. Due to some hormones like growth hormone, corticotropin-releasing hormone, placental lactogen and progesterone secreted by placenta, pregnancy is associated with insulin resistance. When pancreatic function is not sufficient to overcome this insulin resistance, diabetes develops during gestation [1-4]. On this basis, gestational diabetes is defined as onset or first recognition of abnormal glucose tolerance during pregnancy [5]. For the diagnosis of GDM,

screening tests with oral glucose tolerance test (OGTT) are performed during pregnancy. The method and the thresholds of the diagnostic screening tests in GDM have changed according to the results of some recent studies [6-9]. According to the HAPO study [10] in which more than 23,000 pregnancies were evaluated with a 75-gram two-hour oral GTT, the threshold glucose values were determined in respect of infant birth weight, cord C-peptide (proxy for fetal insulin level), and percent of body fat. HAPO study showed us, women with higher threshold experience more complications in contrast to women with lower threshold.

OGTT with 50-gram oral glucose was used generally to screen GDM, in which after one hour of

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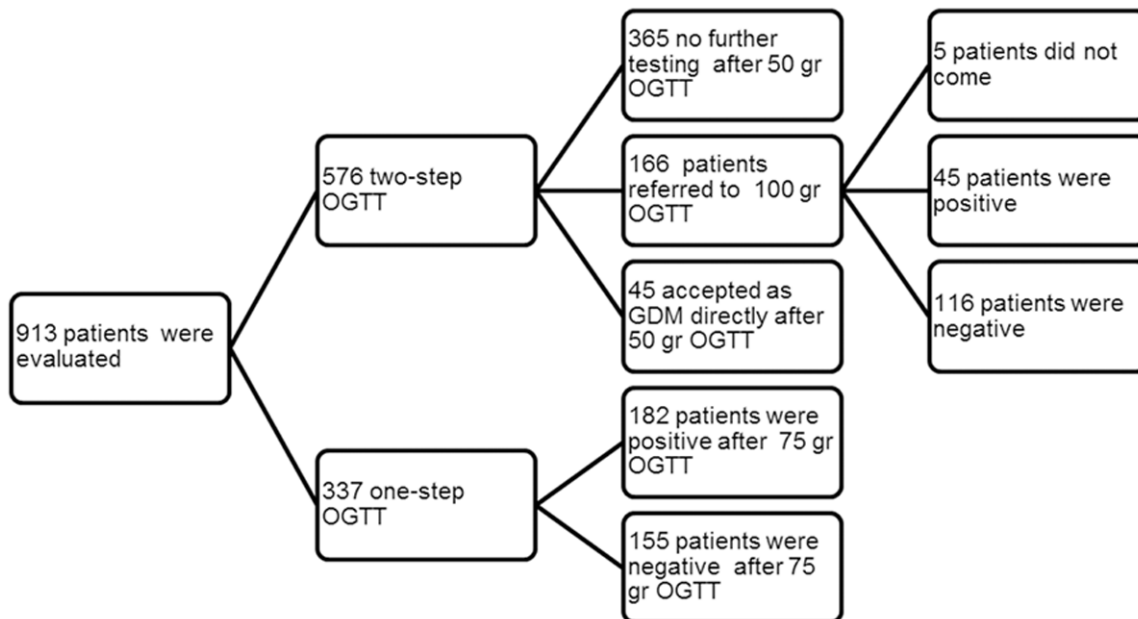


Figure 1. Consort diagram of the study.

Table 1. Results of patients

	75 gram OGTT	50 gram OGTT	100 gram OGTT
Number of patients	337	576	161
Age (years)	28.93±5.6	29.12±5.87	28.09±5.6
HbA1c (%)	5.25±0.56	5.15±0.26	5.24±0.25

Data are mean ± standard deviation. HbA1c: Glycated haemoglobin.

glucose load blood glucose concentration was measured. For a positive screen, the threshold of the first hour blood glucose level is proposed to be ≥ 140 mg/dL. It is suggested to use a lower threshold to have a greater sensitivity. But this can lead to more false positive screening results [11, 12]. According to a systematic review of screening tests for gestational diabetes by the US preventive Services Task Force (USPSTF), at the 130 mg/dL threshold, sensitivity and specificity were found to be 88 to 99 percent and 66 to 77 percent, respectively [13]. In general practice patients with blood glucose level < 140 mg/dl at first hour of 50 gr GTT are accepted as normal and do not need any further testing. On the other hand the patients with blood glucose levels > 180 mg/dL at first hour are accepted directly to have GDM and are followed as GDM thereafter. Only those with blood glucose levels between 140-180 mg/dl are requested to proceed to 100 gr OGTT. The diagnostic threshold values for GDM in 100 gr OGTT are accepted as 95 mg/dl, 180 mg/dl,

155 mg/dl and 140 mg/dl at fasting, first, second and third hours respectively. Two values above these levels are required for diagnosis [14, 18].

A OGTT with 75-gram glucose for two hours is also recommended as one step screening test for GDM diagnosis. There is no consensus regarding the optimum thresholds for a positive test [15]. The most commonly used thresholds for defining elevated values have been proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). According to this, the diagnostic threshold values for GDM are accepted in 75 gram OGTT as 92 mg/dl, 180 mg/dl, 153 mg/dl at fasting, first and second hours respectively. Only one positive value is required for the diagnosis.

Glycated haemoglobin (HbA1c) used to be a follow-up parameter in diabetes as it is thought to reflect chronic glycemia [14, 18]. However, its role in the diagnosis of diabetes is being discussed. But the use of HbA1c in the diagnosis of GDM is not well determined. Variations of HbA1c measurement, creates also a problem for use of HbA1c in routine clinical practice [10, 16]. On this basis we aimed in our study to evaluate the relation of HbA1c and blood glucose levels of 75 gram (one step) and 50-100 gram

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Table 2. Correlations analysis of patients

	75 gram OGTT		100 gram OGTT	
	r value	p value	r value	p value
A1c vs fasting plasma glucose	r=-0.45	P=0.596	r=-0.053	P=0.662
A1c vs 1-h post-loaded Plasma glucose	r=0.274	P=0.001	r=-0.019	P=0.875
A1c vs 2-h post-loaded Plasma glucose	r=0.240	P=0.001	r=0.115	P=0.348
A1c vs 3-h post-loaded Plasma glucose	-		r=0.256	P=0.239

Data are mean \pm standard deviation. HbA1c: Glycated haemoglobin.

(two step) GTT in pregnant patients who were screened for GDM.

Materials and methods

After the approval of local ethics committee (ethics committee of Bakırköy Dr. Sadi Konuk Research and Education Hospital) the parameters of 913 pregnant women who were screened for GDM during 24-28th gestational weeks between January 2012 and January 2013 are evaluated retrospectively (**Figure 1**). The two step screening with 50 gram and 100 gram OGTT were used in 576 patients. One step screening with 75 gram OGTT was used in the remaining 337 patients. The screening method was chosen according to doctor preference. HbA1c levels of all patients have been recorded within 3 days after OGTT. The methods of the screening tests and their diagnostic thresholds were performed as mentioned before according to the ADA 2010 guidelines. HbA1c was assessed using the HPLC method with Primus. Glucose levels were measured in venous plasma by Architect 16,200 auto-analyser by Abbot.

SPSS 18.0 was used for statistical analyses. Kolmogorov-Smirnov and Shapiro-Wilkie were used in order to investigate normality of the data. The differences between groups were analysed by Mann-Whitney U test whereas correlation analysis was done with Kendall's Tau method.

Results

The mean age of all patients enrolled in to the study was 28.4 \pm 5.6 (17-46) years. Mean age of 576 patients who have undergone two step screening was 28.09 \pm 5.6 (17-43) years. Whereas the mean age of the group undergone the one step screening was 28.93 \pm 5.6 (17-46) years. Three-hundred-sixty-five of the 576 patients in two-step group did not undergo any

further testing as they were accepted not to have GDM according to 50 gram OGTT results. On the other hand 45 patients got directly the diagnosis of GDM after 50 gr OGTT and did not proceed to 100 gram OGTT. After the first step, 100 gram OGTT is

recommended to 166 patients, but only 161 patients could attend the 2nd step as some of them did not accept or not tolerate the 2nd step. After the second step 45 more patients (28%) got the diagnosis of GDM and the remaining 116 patients (72%) were accepted as not to have GDM. According to 100 gram OGTT (two step) results, patients with blood glucose levels above the threshold limits were 49 patients (30.4) at fasting time, 62 patients (38.5%) at first hour, 49 patients (30.4%) at second hour, 43 patients (26.7%) at third hour. In the 75 gram OGTT (one step) group 182 of the patients (54%) got the diagnosis of GDM after the test. The numbers of patients with blood glucose levels above the limits in one step group were 142 patients (42.1%) at fasting time, 72 patients (21.4%) at first hour, 45 patients (13.4%) at second hour. In the two step group, values of patients with normal glucose levels were compared to the values of patients with glucose levels above the limits at fasting, 1st hour, 2nd hour and third hour separately. According to this comparison the HbA1c levels were not significantly different between patients with normal and high glucose levels. In the one step group, HbA1c levels were also not significantly different between patients with normal and high blood glucose levels at fasting and first hour. But the HbA1c levels of patients with high blood glucose levels at 2nd hour were significantly higher (P=0.038) in comparison to the patients with normal blood glucose levels in 2nd hour of one step group. On the other hand correlation analyses showed no significant relation between any blood glucose level of 100 gram OGTT and HbA1c level. Whereas in 75 gram OGTT 1st and 2nd hour blood glucose levels were found to have a significant relation with HbA1c levels (r=0.274, P=0.001 and r=0.240, P=0.001; respectively) (**Tables 1 and 2**). The significant correlations were shown as a chart in **Figures 2 and 3**.

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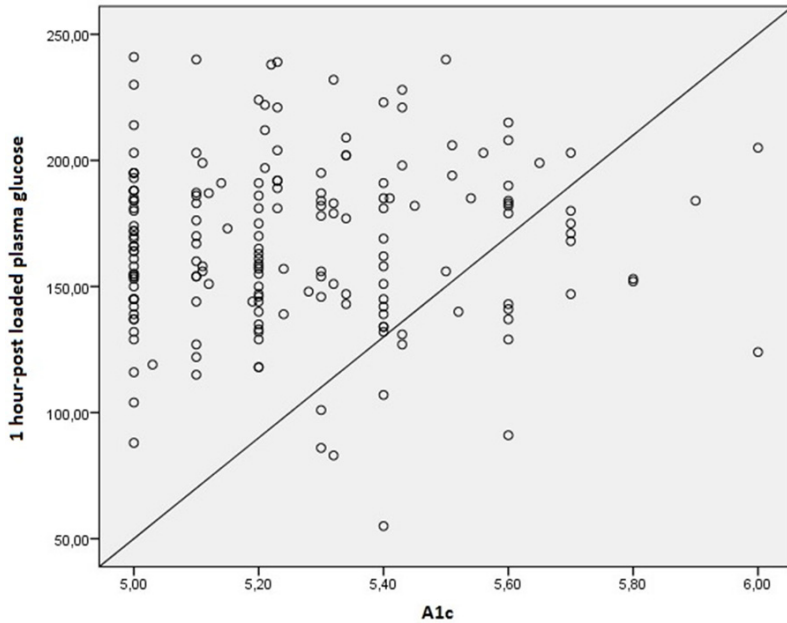


Figure 2. Correlation analysis between HbA1c and 1 hour-post loaded plasma glucose levels.

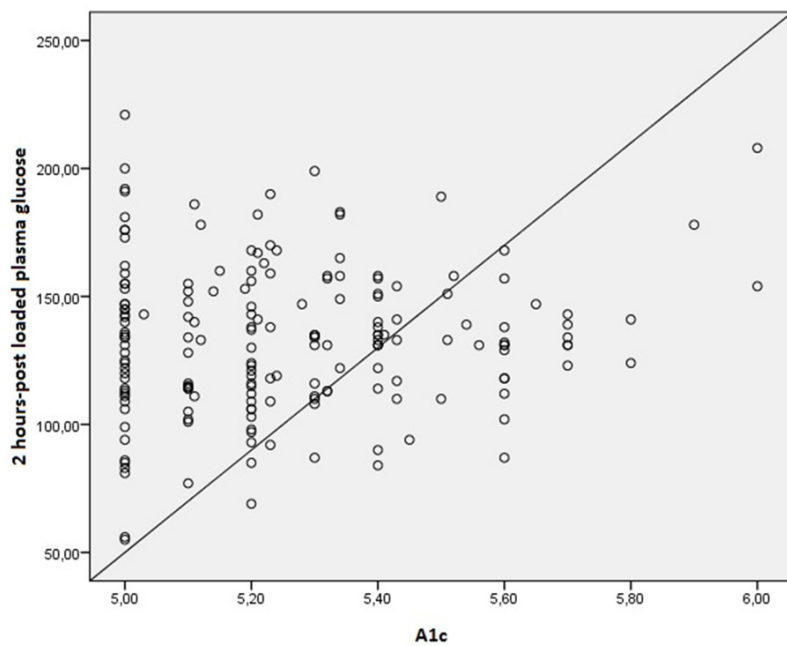


Figure 3. Correlation analysis between HbA1c and 2 hours-post loaded plasma glucose levels.

Discussion

The higher frequency of GDM diagnosis in the one step method is an expected result of our study which supports the discussions of HAPO study [10] that one step approach with 75 gr

OGTT leads to higher frequency of GDM diagnosis.

In last year the diagnostic value of HbA1c in diabetic patients is being discussed more frequently. In different studies HbA1c is found to be correlated with post-loaded glucose concentrations at different hours in non-pregnant people [20]. But the relation of HbA1c with glucose levels of OGTT during GDM screening is not well-known in pregnant women. In the literature different HbA1c thresholds were evaluated for GDM diagnosis. HbA1c thresholds like % 5.0, 5.3, 5.5, and 7.5 were found not to have direct relation with GDM probability [17, 18]. In our study we evaluated the relation between HbA1c and the glucose levels in OGTT during GDM screening. Correlation analysis showed no significant relation between any blood glucose level of 100 gram OGTT and HbA1c level, whereas in 75 gram OGTT 1st and 2nd hour blood glucose levels were found to have a significant relation with HbA1c levels ($P=0.001$, $P=0.001$). The HbA1c levels of patients having high blood glucose levels at 2nd hour in 75 gram OGTT were significantly higher than patients having normal blood glucose levels at 2nd hour of 75 gram OGTT.

It is now generally accepted that, especially in high-risk women, overt diabetes should be excluded at first prenatal visit. However, important increase in the prevalence of GDM and associated costs and workload is the most relevant clinical problem in 75 gram OGTT. Our

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significant result of the study was that in the two step screening group, the frequency of GDM was much more lower (17%) than the GDM frequency in one step group (54%) and this is consistent with the literature. Especially the 75 gram OGTT approach is based on data that increasing glucose levels resulted from a 2-hour post-loaded glucose level are associated with an increasing risk of cesarean delivery, birthweight >90th percentile, neonatal hypoglycemia, and neonatal hyperinsulinism [19]. Due to the increased risk of maternal and fetal complications of GDM, confusion of the diagnosis constitutes significant results in clinical practice.

Conclusion

HbA1c may be used as an important tool in the diagnosis of GDM. But due to the variation of HbA1c in pregnant women and as there is not an absolute cut-off level for HbA1c it may be more reliable to evaluate HbA1c level together with the blood glucose levels in OGTT.

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Disclosure of conflict of interest

None.

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References

- [1] Moyer VA; U.S. Preventive Services Task Force. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; 160: 414-420.
- [2] Getahun D, Nath C, Ananth CV, Chavez MR and Smulian JC. Gestational diabetes in the United States: temporal trends 1989 through 2004. *Am J Obstet Gynecol* 2008; 198: 525, e1-5.
- [3] Dodd JM, Crowther CA, Antoniou G, Baghurst P and Robinson JS. Screening for gestational diabetes: the effect of varying blood glucose definitions in the prediction of adverse maternal and infant health outcomes. *Aust N Z J Obstet Gynaecol* 2007; 47: 307-312.
- [4] Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Aktary WM, Pasichnyk D, Seida JC and Donovan L. Screening and diagnosing gestational diabetes mellitus. *Evid Rep Technol Assess (Full Rep)* 2012; 1-327.
- [5] Proceedings of the 4th International Workshop-Conference on Gestational Diabetes Mellitus. Chicago, Illinois, USA. 14-16 March 1997. *Diabetes Care* 1998; 21 Suppl 2: B1-167.
- [6] American Diabetes Association. Standards of medical care in diabetes-2014. *Diabetes Care* 2014; 37 Suppl 1: S14-80.
- [7] Canadian Diabetes Association Clinical Practice Guidelines Expert C, Thompson D, Berger H, Feig D, Gagnon R, Kader T, Keely E, Kozak S, Ryan E, Sermer M and Vinokuroff C. Diabetes and pregnancy. *Can J Diabetes* 2013; 37 Suppl 1: S168-183.
- [8] Bonongwe P, Lindow SW and Coetzee EJ. Reproducibility of a 75G oral glucose tolerance test in pregnant women. *J Perinat Med* 2015; 43: 333-338.
- [9] Mohan V, Mahalakshmi MM, Bhavadharini B, Maheswari K, Kalaiyarasi G, Anjana RM, Uma R, Usha S, Deepa M, Unnikrishnan R, Pastakia SD, Malanda B, Belton A and Kayal A. Comparison of screening for gestational diabetes mellitus by oral glucose tolerance tests done in the non-fasting (random) and fasting states. *Acta Diabetol* 2014; 51: 1007-1013.
- [10] HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; 358: 1991-2002.
- [11] Carpenter MW and Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 1982; 144: 768-773.
- [12] Coustan DR, Widness JA, Carpenter MW, Rotondo L, Pratt DC and Oh W. Should the fifty-gram, one-hour plasma glucose screening test for gestational diabetes be administered in the fasting or fed state? *Am J Obstet Gynecol* 1986; 154: 1031-1035.
- [13] Donovan L, Hartling L, Muise M, Guthrie A, Vandermeer B and Dryden DM. Screening tests for gestational diabetes: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013; 159: 115-122.
- [14] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva AD, Hod M, Kitzmiller JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33: 676-682.

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- [15] Harlass FE, McClure GB, Read JA and Brady K. Use of a standard preparatory diet for the oral glucose tolerance test. Is it necessary? *J Reprod Med* 1991; 36: 147-150.
- [16] Hanas R, John G; International HBA1c Consensus Committee. 2010 consensus statement on the worldwide standardization of the hemoglobin HBA1C measurement. *Diabetes Care* 2010; 33: 1903-1904.
- [17] Uncu G, Ozan H and Cengiz C. The comparison of 50 grams glucose challenge test, HbHbA1c and fructosamine levels in diagnosis of gestational diabetes mellitus. *Clin Exp Obstet Gynecol* 1995; 22: 230-234.
- [18] Rajput R, Yogesh Y, Rajput M and Nanda S. Utility of HbHbA1c for diagnosis of gestational diabetes mellitus. *Diabetes Res Clin Pract* 2012; 98: 104-107.
- [19] Rebarber A, Dolin C, Fields JC, Saltzman DH, Klauser CK, Gupta S and Fox NS. Screening approach for gestational diabetes in twin pregnancies. *Am J Obstet Gynecol* 2014; 211: 639, e631-635.
- [20] Avignon A, Radauceanu A and Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 1997; 20: 1822-1826.