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The Place of Hba1c Level in Diabetes Mellitus Diagnosis, Comparison with Current Diagnostic Criteria (Hba1c Level in Diabetes Mellitus)

Ulas Isık[1*], Berrin Cetınarslan[2], Cavit Isik Yavuz[3]
[1]MD, Kocaeli State Hospital, Department of Medical Oncology, Kocaeli, Turkey
[2]Professor, Kocaeli University Faculty of Medicine, Internal Medicine, Kocaeli, Turkey
[3]Professor, Hacettepe University, Faculty of Medicine, Department of Public Health, Ankara, Turkey

Abstract: ***Background***: Diabetes mellitus is a long-term metabolic disorder. Early detection is crucial. In recent years, glycated hemoglobin has gained attention as a valuable biomarker for diagnosing diabetes. This study aimed to determine the ability of HbA1c to detect diabetes cases by simultaneously determining HbA1c levels. ***Methods***: This study included a total of 200 patients. It was conducted between February 2010 and February 2011. Of the 200 participants, 23 individuals with fasting plasma glucose levels of 126 mg/dL or higher did not undergo oral glucose tolerance testing. These individuals were classified as having diabetes mellitus. Additional biochemical parameters, including triglycerides, total cholesterol, HDL-C, LDL-C, VLDL-C, and HbA1c. Waist circumference and body mass index were also measured. ***Results***: Of the 200 participants in the study, 141 were female, and 59 were male. There was no statistical difference in gender distribution between the groups. Of the 29 participants mentioned, 22 had diabetes mellitus, four had impaired glucose tolerance, and three were normoglycemic according to oral glucose tolerance testing and fasting plasma glucose. When the HbA1c value was 6.5%, it was observed that its sensitivity in detecting diabetes cases was 47%, and its specificity was 95%. It was determined that there was a positive significant correlation between fasting plasma glucose and first and second-hour oral glucose tolerance testing values and HbA1c (p=0.001 and r=0.48; r=0.37 ve r=0.47 respectively). ***Conclusion***: This study's findings reaffirm the importance of HbA1c as a diagnostic marker for diabetes mellitus, particularly its high specificity and ability to provide a long-term view of glycemic control.

Keywords: Diabetes mellitus, Fasting Plasma Glucose, Oral Glucose Tolerance Tests, Metabolic Syndrome, HbA1c.

Research Paper

***Corresponding Author:**
Ulas Isık
MD, Kocaeli State Hospital, Department of Medical Oncology, Kocaeli, Turkey

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INTRODUCTION

Diabetes mellitus (DM) is a long-term metabolic disorder marked by consistently high blood sugar levels, and it's becoming a growing global health challenge [1]. With its rising prevalence and serious complications, like heart disease, kidney damage, nerve issues, and vision problems, managing the condition effectively hinges on accurate and timely diagnosis [2]. Early detection is crucial because it allows for treatments that reduce the risk of these severe long-term effects [3]. Traditionally, diagnosing DM has relied on fasting plasma glucose (FPG), oral glucose tolerance tests (OGTT), and random plasma glucose measurements [4]. While these methods work well, they have drawbacks, such as short-term fluctuations in blood sugar levels, the need for patients to fast beforehand, and variability due to pre-analytical factors [5].

In recent years, glycated hemoglobin (HbA1c) has gained attention as a valuable biomarker for diagnosing DM [6]. Unlike the traditional methods, HbA1c provides a broader picture by reflecting average blood sugar levels over the past two to three months. It avoids the day-to-day ups and downs of glucose levels

and does not require fasting or drinking glucose solutions, making it more convenient for patients and clinicians [7]. Over the past decade, respected organizations like the American Diabetes Association (ADA)) and the World Health Organization (WHO) have added HbA1c to their diagnostic criteria [8]. However, its use is not without controversy. There is ongoing debate about how sensitive and specific HbA1c is, especially across different populations where genetic or hematological factors can affect accuracy [9].

This article explores the role of HbA1c in diagnosing DM, weighing its benefits and limitations compared to traditional methods. This study aimed to determine the ability of HbA1c to detect DM cases by simultaneously determining HbA1c levels in patients with OGTT indications, comparing the determined threshold value with the threshold value recommended by the ADA, and determining the correlation of HbA1c levels with 1st—and 2nd-hour plasma glucose and the presence of metabolic syndrome during FPG and OGTT.

Material and Methods

Study Population

This study included a total of 200 patients.

Study Design

It was conducted between February 2010 and February 2011 at the Endocrinology and Metabolism outpatient clinic within the Internal Medicine Department at the Faculty of Medicine in Turkey. Participants were adults aged 18 years or older who had no prior diagnosis of overt DM and were referred for oral glucose tolerance testing (OGTT). Of the 200 participants, 23 individuals with fasting plasma glucose (FPG) levels of 126 mg/dL or higher did not undergo OGTT. These individuals were classified as having DM (DM) based on the American Diabetes Association criteria, and their HbA1c levels were recorded. OGTT was performed on the remaining 177 participants, with plasma glucose levels measured at the first and second hours. The glycemic status of the patients was determined as normal, impaired glucose tolerance (IGT) and DM.

During the study, detailed medical histories and physical examinations were completed for all patients. Information such as age, sex, comorbidities, smoking status, medication use, and any history of gestational DM was documented. Anthropometric measurements—including height, weight, and waist circumference—were recorded, and blood pressure was measured in a seated position using the right arm.

Analysis

The requirements for OGTT were thoroughly explained to each participant. On the day of testing, fasting plasma glucose levels were obtained from venous blood samples. Patients then consumed 75 grams of glucose dissolved in 300 mL water within five minutes. During the test, participants remained seated, and blood samples were drawn at the first and second hours to assess plasma glucose and concurrent insulin levels. Additional biochemical parameters, including triglycerides (TG), total cholesterol, HDL-C, LDL-C, VLDL-C, and HbA1c, were measured using fasting blood samples collected the same day. Waist circumference was measured at the level of the umbilicus, and body mass index (BMI) was calculated using the formula weight (kg)/height (m^2). Insulin resistance was evaluated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula [10].

$$\text{HOMA-IR} = \frac{\text{glucose (mg/dL)} \times \text{insulin } (\mu\text{U/mL}) \times 0.056}{22.5}$$

The diagnosis of metabolic syndrome was determined according to the International Diabetes Federation criteria [11]. Plasma glucose levels were measured using the glucose oxidase method on an Abbott Aeroset auto analyzer (Chicago, IL, USA) with Abbott kits. Insulin levels were analyzed via the electrochemiluminescence method using a Roche E-170 analyzer (Basel, Switzerland). Total cholesterol was measured using the cholesterol oxidase method on the Abbott Aeroset auto analyzer, while LDL-C was calculated using the Friedewald formula [12]. HDL-C was determined using Abbott kits on the Abbott Aeroset autoanalyzer. Triglycerides were measured using the glycerol oxidase method, and VLDL-C levels were calculated using the Friedewald formula:

$$\text{LDL-C} = \text{Total Cholesterol} - (\text{VLDL-C} + \text{HDL-C})$$

HbA1c levels were analyzed on a Shimadzu SPD-20 AV HPLC system with ClinRep columns.

Exclusion Criteria

- Patients with anemia
- Hemoglobinopathies
- Renal insufficiency
- Pregnant participants
- Individuals under 18

Ethics

Ethical approval was obtained from the Ethics Committee. XXX University Faculty of Medicine Ethics Committee, Decision No: KKAEK 2010/17 (Date: 02/02/2010). The study adhered to the principles outlined in the Declaration of Helsinki. Participation was voluntary, with informed consent obtained from all patients, who were assured that their data would be used solely for research purposes, and strict confidentiality was maintained.

Statistical Analysis

Statistical analysis was conducted using SPSS for Windows, version 11.0. Numerical data were presented as mean ± standard deviation, while categorical data were summarized as frequencies and percentages. Group comparisons were performed using ANOVA with post-hoc Bonferroni tests and Pearson correlation analysis. Categorical data comparisons employed the Chi-square test, with statistical significance set at $p < 0.05$. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of HbA1c were calculated using 2×2 contingency tables, with OGTT as the gold standard. Receiver operating characteristic (ROC) curves for HbA1c cut-off values were also generated using SPSS.

RESULTS

The study included a total of 200 participants, of whom 141 were female and 59 were male. No statistically significant difference was observed in gender distribution between the groups. The oldest group was the DM group. The mean age of the group was 53.4±11.7. The group with higher systolic and diastolic pressures was the DM group. Total cholesterol, LDL and HbA1c values were higher in the IGT group than in the other groups. In the analyses, age, systolic and diastolic blood pressure, waist circumference and HbA1c variables showed significant differences between the groups. No significant differences were found for the others (p<0,05). (Table 1).

Table 1: Demographic and Laboratory Characteristics of Participants

	Normoglycemia	IGT	DM	p
Age	42±13.7	48.7±12	53.4±11.7	**0.001**
Systolic (mmHg)	133.7±14.8	142±6	144.6±18.2	**0.001**
Diastolic (mmHg)	75.8±11.3	83.1±13.1	83.1±10.9	**0.001**
MBI (kg/m²)	33.5±8.2	36.2±6.6	34.4±6.2	0.109
Total Cholesterol (mg/dl)	199.7±45	216.9±43.6	213.1±48.2	0.057
LDL (mg/dl)	128±34.9	136.2±37.8	131.3±39.7	0.432
HDL mg/dl	45.8±11.9	45±10.4	43.1±8.6	0.365
Trigliserit (mg/dl)	153.2±125.6	175.8±82.4	193.1±87.2	0.099
Waist Circ. (cm)	100.6±15.4	106.8±12	105.3±14.6	**0.031**
HbA1c (%)	5.4±0.5	5.6±0.6	6.3±0.5	**0.001**

Among the participants, 29 had an HbA1c value of ≥6.5%. Of these, 23 were female and six were male. Analysis revealed that based on OGTT and FPG criteria, 22 of these individuals were diagnosed with DM, four were identified as having IGT, and three were normoglycemic.

The sensitivity, specificity, PPV, and NPV of an HbA1c threshold of 6.5% in diagnosing diabetes were calculated as follows: sensitivity 47%, specificity 95%, PPV 75%, and NPV 85%. The sensitivity, specificity, PPV, and NPV of an HbA1c threshold of 5.5% are as follows: 97%, 51%, 37%, and 98%, respectively. The threshold of 7.0% is as follows: 6%, 99%, 71%, and 78%, respectively. As the Threshold Value (HbA1c) value increases, specificity and PPV values increase proportionally while others decrease. Sensitivity and specificity values at various HbA1c thresholds are presented in Table 2, and the corresponding ROC curve is illustrated in Figure 1.

Table 2: Sensitivity, Specificity, PPV, and NPV at Different HbA1c Thresholds

Threshold Value (HbA1c)	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)
5.5	97	51	37	98
5.6	95	59	41	97
5.7	89	62	41	95
5.8	84	68	44	93

5.9	80	75	50	92
6.0	69	79	50	89
6.1	63	85	55	88
6.5	47	95	75	85
7.0	6	99	75	78

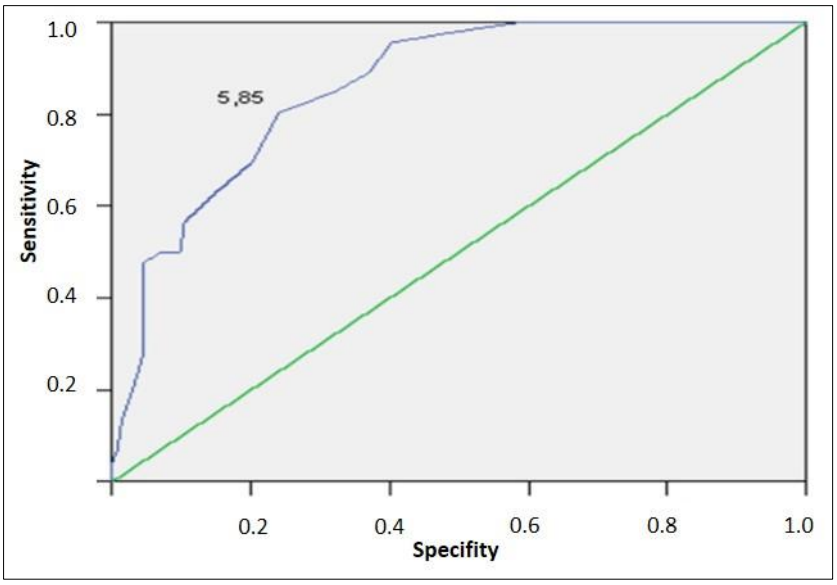


Figure 1: ROC Curve of HbA1c Values

The diagnostic capability of OGTT values at the first hour for thresholds of ≥140 mg/dL and ≥200 mg/dL was evaluated in identifying diabetes cases. As the Threshold Value (HbA1c) value increases, specificity and PPV values increase proportionally while others decrease. The sensitivity, specificity, PPV, and NPV for these thresholds were calculated and are detailed in Table 3.

Table 3: The role of first hour of OGTT in the Diagnosis of DM

Threshold Value (OGTT)	Sensitivity (%)	Specify (%)	PPV (%)	NPV (%)
140	96	30	19	93
200	69	73	97	30

The relationship between HbA1c and glycemic indices, including FPG and OGTT values, was analyzed. A significant positive correlation was identified between HbA1c and FPG and between HbA1c and first—and second-hour OGTT values (p=0.001, with correlation coefficients of r=0.48, r=0.37, and r=0.47, respectively). Figure 2 provides a graphical representation of these correlations.

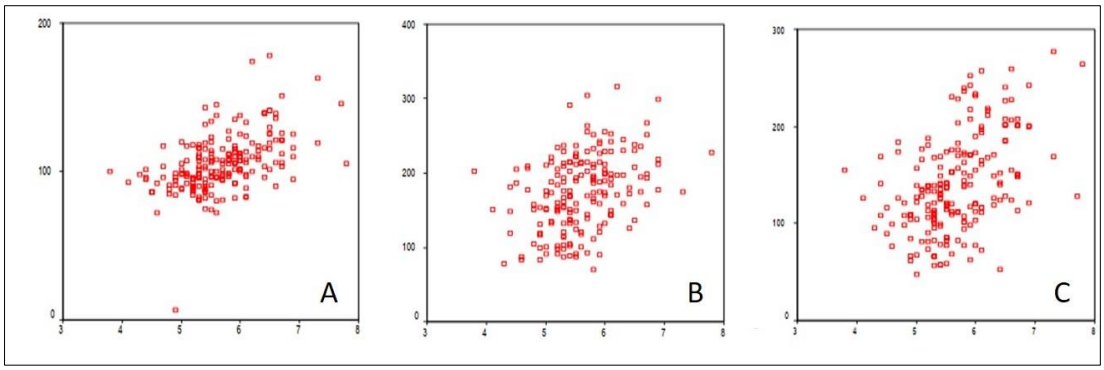


Figure 2: Correlation between HbA1c and FPG/OGTT. A: FPG; B: OGTT 1 hour; C: OGTT 2 hour

DISCUSION

According to the data obtained in the article, Age, systolic and diastolic blood pressure, and HbA1c values showed significant differences in the normoglycemia, IGT, and DM groups. There was no difference between the groups in MBI, Total Cholesterol, LDL, HDL, and Triglyceride values. A positive, significant correlation was determined between FPG and first—and second-hour OGTT values and HbA1c.

While the HbA1c value was 6.5%, its sensitivity in detecting DM cases was 47%, its specificity was 95%, its positive predictive value was 75%, and its negative predictive value was 85%. The present study provides valuable insights into the role of HbA1c in diagnosing DM and its comparison with established diagnostic criteria, including FPG and OGTT. The findings underscore significant variations in age, systolic and diastolic blood pressure, and HbA1c levels across the normoglycemia, IGT, and DM groups, while metabolic parameters such as BMI, total cholesterol, LDL, HDL, and triglyceride values remained comparable. These results provide a nuanced perspective on the clinical utility of HbA1c as a diagnostic tool.

The observed positive correlation between HbA1c and FPG and OGTT values further supports the contention that HbA1c reflects cumulative glycemic exposure and is thus a robust indicator of chronic hyperglycemia. This finding aligns with previous literature, such as the landmark studies by Selvin *et al*., [13], and Hoffmann *et al*., [14], demonstrating that HbA1c effectively captures long-term glycemic trends and correlates strongly with OGTT and FPG values. The concordance of HbA1c with other glycemic indices underscores its utility in diagnosing and monitoring DM while circumventing the temporal variability inherent to FPG and OGTT measurements.

Of particular significance is the diagnostic performance of the HbA1c threshold of 6.5%, which exhibited a high specificity (95%) and acceptable positive predictive value (75%) but a comparatively modest sensitivity (47%) for detecting DM. These findings are consistent with reports by the International Expert Committee [15], and Nguyen *et al*., [16], who documented that using HbA1c as a diagnostic criterion provides high specificity but may underdiagnose early DM or IGT cases. The same results are confirmed by recent articles [17, 18]. Such limitations may arise from variability in glycation rates influenced by genetic, racial, or physiological factors, as Herman *et al*., [19], and Karter *et al*., [20], discussed.

Notably, the lack of significant differences in lipid profiles and BMI among the normoglycemic, IGT, and DM groups suggests that these parameters may not be reliable discriminators for DM in the studied cohort. This observation is corroborated by findings in prior research, such as the study by Unwin *et al*., [21], and Liu *et al*., [22], which highlights that dyslipidemia often manifests later in the disease course or is the primary cause of poorly controlled DM, limiting its diagnostic applicability during the early stages.

The high negative predictive value (85%) of HbA1c in the present study underscores its clinical utility in ruling out DM, especially in populations with a low pretest probability. However, the suboptimal sensitivity necessitates caution in using HbA1c as a sole diagnostic criterion, particularly in high-risk individuals or populations with suspected IGT, where additional confirmatory testing such as OGTT may be warranted. This aligns with the recommendations of the ADA, which emphasizes a multi-modal diagnostic approach tailored to individual risk profiles.

Despite the methodological rigor of this study, several limitations should be acknowledged. First, while the sample size of 200 participants is adequate for a preliminary analysis, it may not be large enough to ensure broad generalizability across diverse populations. The study's single-center design also limits external validity, as regional and demographic variations in metabolic responses could affect the diagnostic accuracy of HbA1c. Moreover, the reliance on a one-year data collection period restricts the ability to assess long-term fluctuations in HbA1c levels and their implications for diabetes diagnosis. Additionally, excluding 23 individuals with FPG levels of 126 mg/dL or higher from undergoing an OGTT may introduce classification bias and hinder comparative assessment between different diagnostic criteria.

In conclusion, this study's findings reaffirm the importance of HbA1c as a diagnostic marker for DM, particularly its high specificity and ability to provide a long-term view of glycemic control. Nonetheless, the limited sensitivity observed in this and similar studies underscores the need for complementary diagnostic tools to identify early-stage DM accurately. Future research should address population-specific variations in HbA1c performance and integrate it with other biomarkers to enhance diagnostic precision.

Availability of Data and Materials: It may be requested from the Corresponding Author with appropriate justification.

Ethical Approval: Kocaeli University Faculty of Medicine Ethics Committee, Decision No: 02.02.2010 KKAEK 2010/17.

Informed Consent: It was taken verbally from the participants.

Declaration of Interests: No declaration of Interest.

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