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Original Research

The Compatibility of Hemoglobin A1c with Oral Glucose Tolerance Test and Fasting Plasma Glucose

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Abstract

Objectives: Diabetes mellitus (DM) is a chronic metabolic disease requiring lifelong medical care, and its prevalence is increasing worldwide. Early diagnosis of prediabetes and diabetes is significant in view of the mortality, morbidity and cost associated with them. Because of the difficulties in application and reproducibility of oral glucose tolerance test (OGTT), which is considered to be the gold standard in the diagnosis of DM, more feasible diagnostic tests are needed. This study aims to evaluate the validity of hemoglobin A1c (HbA1c) in predicting prediabetes and diabetes in the Turkish population and to evaluate the compatibility of HbA1c with other diagnostic tests.

Methods: The patients who were admitted to Health Sciences University Sisli Hamidiye Etfal Training and Research Hospital internal diseases and endocrinology outpatient clinics between 01.01.2013 and 30.06.2014 enrolled in this study. The participants were >18 years of age and were not diagnosed with prediabetes or DM earlier. The results of OGTT, fasting plasma glucose (FPG) and HbA1c tests were retrospectively screened, and the correlation of them was analyzed.

Results: In this study, 201 participants enrolled. Of these cases, 127 were women and 74 were men. Mean age of the group was 49.3±10.4 years. HbA1c was observed <5.7% in the 15%, 5.7-6.4% in the 60%, and ≥ 6.5% in the 25% of the cases. While FPG was <100 mg/dL in 24% of the participants, it was found to be between 100-126 mg/dL in 71% and ≥126 mg/dL in 5% of the participants. According to the OGTT data, 23% of the cases were healthy, 59% were prediabetic and 18% were diabetic. The sensitivity and specificity of HbA1c were calculated as 50% and 80%, respectively. While the sensitivity of FPG was 17% and specificity was 97%.

Conclusion: The data obtained from our study show that HbA1c is a more sensitive test compared to FPG in the diagnosis of DM. Prospective studies with broad participation at national and international levels are needed to redefine HbA1c cut-off points for the diagnosis of DM and prediabetes. Thus, it will be possible to revise the diagnostic guidelines accordingly.

Keywords: Diabetes mellitus; fasting plasma glucose; hemoglobin A1c; oral glucose tolerance test.

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Diabetes mellitus (DM) is a chronic disease of metabolism that requires continuous medical care and the most common endocrine disease in the world. Due to insulin deficiency or defects in insulin effect, subsequently the organism cannot benefit sufficiently from carbohydrates, fats and proteins.[1] Recent studies have shown that the prevalence of DM is increasing worldwide; and that diabetes-related deaths and health expenditures expose social, financial and health systems to a considerable burden.[2] Early diagnosis of the prediabetes and diabetes is significant considering the mortality, morbidity and the costs they may cause. Due to the difficulties in the implementation and reproducibility of the oral glucose tolerance test (OGTT), which is accepted as the gold standard in the diagnosis of DM, more easily applicable diagnostic tests are needed.

In recent years, the use of hemoglobin A1c (HbA1c) in the diagnosis of diabetes mellitus has become widespread due to its practicality and being included in the diagnostic criteria of diabetes mellitus by The World Health Organization (WHO) and ADA.[3] However, in order for Hba1c to be used as a diagnostic test in diabetes mellitus, the standardization of measurement method should be provided as suggested by ADA.[4] In our study, we aimed to understand the validity of HbA1c in predicting diabetes and prediabetes in Turkish society and to evaluate the compatibility of HbA1c with other diagnostic tests.

Methods

Between 01.01.2013 and 06.30. 2014, non-pregnant patients over the age of 18 who were not diagnosed with diabetes and prediabetes who applied Health Sciences University Sisli Hamidiye Etfal Training and Research Hospital internal medicine and endocrinology outpatient clinic were included in this study. Individuals who underwent OGTT for any indication, and the patients whose fasting plasma glucose (FPG) and HbA1c levels were measured were retrospectively screened and the compatibility between OGTT results and FPG and HbA1c measurements was investigated. Cases with non-glycemic factors that may affect HbA1c levels were excluded from this study.

Since the exposure of hemoglobin to glucose will decrease in the presence of factors shortening erythrocyte life span, lower, and erroneous HbA1c values may be detected. Therefore, people with known diagnoses of haemolytic anemia and hypersplenism were not included in this study. Since the duration of exposure of hemoglobin to glucose will increase in cases where erythrocyte life span is prolonged, even though the glycemic regulation is actually normal, erroneously higher HbA1c values may be detected. Therefore, patients with chronic disease anemia, nutritional anemia (due to iron, folate, B12 deficiency), splenectomized individuals, patients with a history of ethilism, and patients who had suffered from acute blood loss (except for menstrual bleeding in the physiological amount) in the last three months were also excluded from this study.

Since liver and kidney failure have complex effects on hemoglobin and HbA1c levels, patients who received these diagnoses and pregnant women were excluded from this study. To differentiate the cases with the abovementioned exclusion criteria, hospital files, drug reports and prescribed drug records of the participants' were retrospectively screened. In addition, information related to hemogram, serum iron, total iron-binding capacity, ferritin, vitamin B12 , folic acid, C reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), urea and creatinine values were also retrospectively screened. In this study, 201 cases aged between 22-77 years, including 127 female, and 74 male patients, who met these criteria were included in this study group.

Ethics committee approval was received from the Health Sciences University Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee for our study (decision date/no: 06.05.2018/1009).

HbA1c measurements were made in the biochemistry laboratory of our hospital with the method of "boronate affinity high-performance liquid chromatography" on the Premier Hb9210 HPLC device. This method also enabled differentiation of the abnormal hemoglobin types, such as HbS, and HbC. Intraassay coefficients of variation (CVs) were 0.9% for HbA1c 5.5%, 1.12% for HbA1c 11.45%, while interassay CVs were 2.54% for HbA1c 5.4%, and 3.04% for HbA1c 10.5%. Plasma glucose measurements were made using a spectrophotometric method.

OGTT was performed with 75 grams of oral glucose intake in the morning after at least three days of carbohydrate (≥150 g/day) diet, and at least eight hours of fasting. According to World Health Organization (WHO) and 2018 ADA criteria plasma glucose measurements were made at 0 min (fasting), and 60 min and 120 min after oral glucose intake.[4, 5] People who had FPG levels of ≥126 mg/dL at least eight hours after fasting, and 120-minute plasma glucose of ≥ 200 mg/dL or HbA1c of ≥6.5 at OGTT were considered as having diabetes mellitus. Patients with FPG of 100-125 mg/dL were classified in the impaired fasting glucose (IFG) and patients with plasma glucose of 140-199 mg/dL 120 minutes after OGTT in the impaired glucose tolerance (IGT) group. The cases with HbA1c levels between 5.7-6.4% were considered as prediabetic patients (IFPG + IGT).

Statistical Analysis

SPSS 22.0 program was used in statistical analyses. Mean standard deviation, median, minimum, maximum, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured using Kolmogorov -Smirnov test. In the analysis of quantitative data, Kruskal-Wallis, Mann-Whitney U test and independent samples t- test were used. In the analysis of qualitative data, chi-square test was used. Kappa goodness –of-fit fit test was used for contingency analysis. P-value of <0.05 was considered statistically significant.

Results

In our study, data of 437 patients were reached. Considering the exclusion criteria, a total of 201 patients consisting of 74 (37%) male, and 127 (63 %) female cases were included in this study. The mean age of the patients was calculated as 49.3±10.4 years. The demographic data of the patients are shown in Table 1.

It was observed that the HbA1c level of 201 patients included in this study was between 5.1% and 11.4 percent. Median and mean HbA1c values were both measured as 6.2 percent. HbA1c values were <5.7% in 14%, 5.7-6.4% in 60%, and 6.5 6.5% in 25% of the cases.

These groups were evaluated as having normal glycemic levels, prediabetes and diabetes mellitus, respectively. In 24% of the participants, fasting plasma glucose was measured within the normal range (<100 mg/dL), while in 71% of the cases, it was between 100-126 mg/dL and these patients were evaluated as having impaired fasting glucose levels. Five percent of these cases were diagnosed with DM because FPG was detected as ≥126 mg/dL. OGTT 0 min plasma glucose values were measured between 81-241 mg/dL, and the median and mean values were 107 mg/dL and 107.9 mg/dL, respectively. It was observed that these values are compatible with FPG values.

When the 0-minute glucose levels in OGTT of the patients included in this study were evaluated, 32% of them were healthy, 61% of them were diagnosed as having impaired plasma glucose (IPG) and 7% with DM. When the plasma glucose values measured at 120 min following OGTT were examined, 51% of the individuals included in this study were healthy, while 32% and 17% of them were determined as having IGT and DM, respectively. When the glycemic data obtained at the 0th and 120th min in OGTT were evaluated in combination, it was seen that 23% of the patients were healthy, 59% of them had IFG and/or IGT, and 18% were diagnosed with DM.

When the cases included in this study were classified as normal, prediabetic or diabetic according to HbA1c levels, the lowest, highest, mean and median values of the fasting

Table 1. Minimum, maximum, mean, and median values of the demographic and biochemical variables

n=201	Range	Median	Mean±SD
Age	22.0-77.0	50.0	49.3±10.4
Creatinine(mg/dL)	0.5-1.2	0.8	0.8±0.2
e-GFR (ml/min/1.73 m^2)	61.6-127.1	95.6	94.0±13.6
AST (U/L)	10.0-54.0	20.0	21.3±7.3
ALT (U/L)	8.0-98.0	23.0	26.5±14.7
FERRİTİN (mg/L)	15.6-782.0	68.6	88.9±80.5
B12 (pg/ml)	201.0-2000.0	351.0	400.2±218.1
Folate (ng/mL)	4.5-20.0	9.3	10.0±2.9
CRP (mg/L)	1.0-9.2	3.2	4.1±1.7
hb (g/dL)	13.0-17.1	14.1	14.4±1.0
Total Cholesterol (mg/dL)	98.0-332.0	211.0	212.3±42.9
Triglyceride (mg/dL)	1.7-523.0	139.0	154.0±82.4
HDL (mg/dL)	23.0-88.0	48.0	50.5±13.3
LDL (mg/dL)	18.0-225.8	130.2	130.9±38.3

e-GFR: Estimated glomerular filtration rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: c-reactive protein; hb: Hemoglobin; HDL: high- density lipoprotein; LDL: low- density lipoprotein; Mean±SD: Mean±Standard Deviation.

Table 2. Minimum, maximum, mean and median FPG (mg/dL) and PG (mg/dL) values at 0., 60. and 120.min of OGTT in normal/ prediabetes/diabetes groups according to HbA1c values

	Min.-Max.	Median	Mean±SD
FPG (mg/dL)			
HbA1c			
Normal	83.0-118.0	107.0	104.5±9.4
Prediabetes	75.0-131.0	107.0	105.9±10.5
Diabetes	85.0-222.0	109.0	112.0±21.2
OGTT 0. min (mg/dL)			
HbA1c			
Normal	82.0-126.0	102.0	103.9±10.8
Prediabetes	81.0-148.0	104.0	105.4±10.9
Diabetes	88.0-241.0	114.0	116.1±22.2
OGTT 60. min(mg/dL			
HbA1c			
Normal	96.0-282.0	178.0	177.1±58.3
Prediabetes	112.0-284.0	192.5	192.5±43.6
Diabetes	139.0-326.0	236.5	225.7±50.0
OGTT 120. min (mg/dL)			
HbA1c			
Normal	82.0-264.0	140.0	141.2±42.4
Prediabetes	49.0-262.0	130.0	140.5±43.4
Diabetes	47.0-280.0	149.5	153.4±61.9

FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test; HbA1c: Hemoglobin A1c; Mean±SD: Mean±Standard Deviation.

plasma glucose, and glycemic levels at 0th, 60th and 120th min of OGTT test in these groups are summarized in Table 2. While the sensitivity and specificity of fasting plasma glucose compared to OGTT were 17% and 97%, its positive and negative predictive values were calculated as 55% and 84%, respectively (Fig. 1). Sensitivity and specificity of HbA1c relative to OGTT were calculated as 50% and 80%, respectively. While its positive, and negative predictive values were 35%, and 88%, respectively (Fig. 2).

Discussion

In our study, the sensitivity and specificity of the HbA1c in diagnosing diabetes were 50% and 80%, respectively. There was a significant agreement ($p<0.0001$) between OGTT and HbA1c in predicting diabetic patients. In a study conducted in the Netherlands with 2753 participants on a national scale, HbA1c was reported to have 24% sensitivity and 99% specificity.[6] In the United States (USA), the study of the "National Health And Nutrition Examination Survey" (NHANES) conducted by Guo et al. with 2593 participants, the diagnostic sensitivity and specificity of HbA1c were calculated as 43% and 99%, respectively.[7]

Similarly, in a cross-sectional study conducted with 1128 patients in China, it was stated that HbA1c has low sensitivity (33.2%) and high specificity (93.5%) in patients diagnosed with DM base on OGTT results.[8] In the research

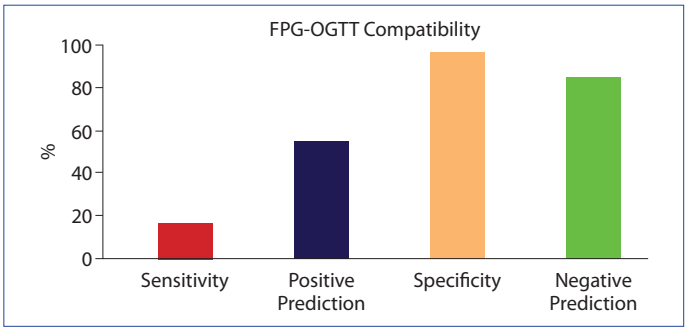

Figure 1. Graphical comparison of the sensitivity, specificity, positive and negative predictive values of the FPG compared to OGTT.

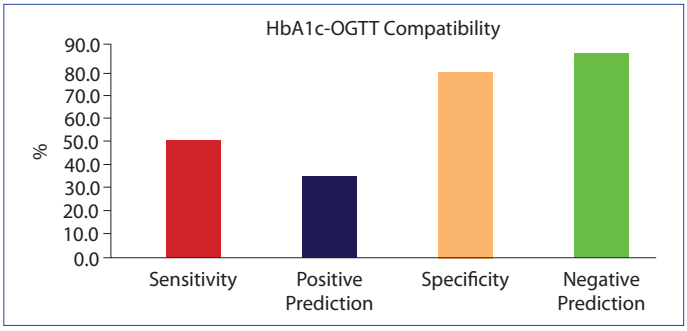

Figure 2. Graphical comparison of the sensitivity, specificity, positive and negative predictive values of HbA1c compared to OGTT.

study conducted by Kumar et al.,[9] HbA1c was found to have 65% sensitivity and 88% specificity in diagnosing diabetes. In the present study, in which we aimed to understand the validity of HbA1c in predicting diabetes in Turkish society, we see that the diagnostic sensitivity of HbA1c is higher and its specificity is lower compared to many studies with wider participation performed in various populations. However, when the available findings are evaluated, HbA1c, with the cut-off value (>6.5%) currently used in the diagnosis of DM, has a weak diagnostic sensitivity in differentiating patients; however, we may say that it has a higher specificity in distinguishing healthy individuals from patients.

In our research study, the sensitivity and specificity of FPG were calculated as 17% and 97%, respectively. With 50% diagnostic sensitivity, HbA1c was found to be stronger than FPG, while it was weaker concerning diagnostic specificity. Contrary to our findings, it was reported that HbA1c had a lower diagnostic sensitivity compared to FPG in a study conducted by retrospectively examining clinical and laboratory information of 35624 patients in Korea.[10, 11]

In our DM screening study, HbA1c could only predict 25% of diabetic, but higher proportion (60%) of the prediabetic patients. On the other hand, measurements of plasma glucose values at 0th and 120th minutes of OGTT could identify 18% of DM and 59% of prediabetic patients. However, FPG could identify 71% of prediabetic, but only 5% of the diabetic individuals. In "The Insulin Resistance Atherosclerosis Study" (IRAS) study conducted on 1008 people in the USA, the incidence of diabetes was found to be 32% based on HbA1c measurements.[12] In addition, in a study conducted by Kim et al.,[13] when the cases were evaluated based on HbA1c levels, a significant increase was observed in the number of prediabetic individuals.

In studies conducted in Europe and China, it has been shown that higher number of prediabetic individuals could be identified based on HbA1c measurements.[14, 15] In contrast, in the NHANES study, the number of prediabetic patients diagnosed based on FPG values was higher than patients detected with HbA1c.[16, 17] We thought that this contrast in studies might be based on ethnic differences. Herman et al. previously reported that the HbA1c level was higher in Asians than other races.[18] In their studies, Okosun et al. detected higher HbA1c values on an average in black people living outside Latin America.[19] This may be due to the variations in erythrocyte half-life and glycation among races and ethnic groups.[20]

The increase in body mass index (BMI) is thought to be another parameter affecting the level of HbA1c. In a study conducted by Incani et al. with obese people, HbA1c val-

ues were shown to be significantly higher (p<0.0001) than nonobese individuals.[21] In our retrospective study, we could not include this parameter because of the missing information about the height and weight of the patients. Therefore, we could not evaluate the relationship between HbA1c and BMI.

Our study has some limitations. First of all, there is a restricted access to some data, such as BMI, due to the retrospective nature of our study and missing records. In addition, since this study had not a prospective design, long-term follow-up of the patients could not be realized and changes in laboratory values could not be observed. In conclusion, HbA1c measurement is an easier, faster and reproducible test compared to OGTT and FPG. As its advantage, it is not affected by satiety or the previous meal. The most significant disadvantage of using HbA1c in the diagnosis of DM is that worldwide laboratory standardization is not fully achieved. Besides, HbA1c is affected by factors, such as ethnicity, BMI, and there are debates about its cut-off values.

The data we obtained from our study have shown that HbA1c is a more sensitive test in the diagnosis of DM compared to FPG. It is also possible to say that HbA1c is a more successful test in differentiating healthy individuals than identifying diabetic individuals. Based on this, we can say that the determination of a cut-off value for HbA1c is not quite sufficient for the diagnosis of diabetes. Prospective studies with wider participation on a national/international scale are needed to redefine diagnostic HbA1c cut-off values for prediabetes and DM and to revise diagnostic guidelines accordingly.

Disclosures

Ethics Committee Approval: Ethics committee approval was received from the Health Sciences University Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee for our study (decision date/no: 06.05.2018/1009).

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Conflict of Interest: None declared.

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