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Measurement Uncertainty of HbA1c and Glucose Parameters, Which Are Diabetes Mellitus Diagnostic Tests

Diabetes Mellitus Tanı Testleri Olan HbA1c ve Glukoz Parametrelerinin Ölçüm Belirsizliği

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Abstract

Objective: In this study, it was aimed to calculate the measurement uncertainties of HbA1c and glucose parameters, which have important roles in the diagnosis and treatment of diabetes, and to evaluate the possible effects of these uncertainty values on clinical decision limits.

Methods: The measurement uncertainties of HbA1c and glucose tests were calculated according to ISO/TS 20914 guidelines. In 2022, the results of patients in whom HbA1c and glucose were ordered simultaneously were retrospectively analysed and the results were evaluated according to measurement uncertainty.

Results: The calculated measurement uncertainty values of HbA1c and glucose tests were 2.41% and 7.92% for level 1 and 1.37% and 7.68% for level 2, respectively. When the HbA1c results of the patients were evaluated according to the measurement uncertainty calculated for level 1 and level 2, 2493 (8.1%) and 1845 (5.9%) were in the grey zone according to negative uncertainty and 2816 (9.1%) and 2120 (6.9%) were in the grey zone according to positive uncertainty, respectively. When glucose results were evaluated according to negative and positive uncertainty at both levels, 3959 (12.8%) and 5934 (19.2%) patients were in the grey zone, respectively.

Conclusion: In our laboratory, uncertainty values calculated for the HbA1c parameter were below the TEa% values determined by all three international organizations. Although the uncertainty of the glucose test was below the CLIA and rilibak TEa% values, it was found to be higher than the BV TEa% value. It should be kept in mind that measurement uncertainty in values at medical decision levels may affect the diagnosis and treatment of DM.

Keywords: Diabetes, glucose, HbA1c, measurement uncertainty

Öz

Amaç: Bu çalışmada diyabetin tanı ve tedavisinde önemli yeri olan HbA1c ve glukoz parametrelerinin ölçüm belirsizliklerinin hesaplanması ve bu belirsizlik değerlerinin klinik karar limitlerine olası etkilerinin değerlendirilmesi amaçlanmıştır.

Yöntem: HbA1c ve glikoz testlerinin ölçüm belirsizlikleri ISO/TS 20914 kılavuzuna göre hesaplandı. 2022 yılında eş zamanlı olarak HbA1c ve glukoz istenen hastaların sonuçları retrospektif olarak incelendi ve sonuçlar ölçüm belirsizliğine göre değerlendirildi.

Bulgular: HbA1c ve glukoz testlerinin hesaplanan ölçüm belirsizliği değerleri seviye 1 için sırasıyla %2,41 ve %7,92, seviye 2 için ise %1,37 ve %7,68 olarak hesaplandı. Hastaların HbA1c sonuçları seviye 1 ve seviye 2 için hesaplanan negatif belirsizliğe göre değerlendirildiğinde sırasıyla 2493'ü (%8,1) ve 1845'i (%5,9), pozitif belirsizliğe göre ise 2816'sı (%9,1) ve 2120'si (%6,9) gri bölgedeydi. Glukoz sonuçları her iki seviyede negatif ve pozitif belirsizliğe göre değerlendirildiğinde sırasıyla 3959 (%12,8) ve 5934 (%19,2) hasta gri bölgede bulundu.

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Öz

Sonuç: Laboratuvarımızda HbA1c parametresi için hesaplanan belirsizlik değerleri her üç uluslararası kuruluş tarafından belirlenen TEa% değerlerinin altında kalmıştır. Glukoz testinin belirsizliği ise CLIA ve rilibak TEa% değerlerinin altında olmasına rağmen BV TEa% değerinden yüksek bulunmuştur. Tıbbi karar düzeylerindeki değerlerde ölçüm belirsizliğinin DM'nin tanı ve tedavisini etkileyebileceği unutulmamalıdır.

Anahtar Kelimeler: Diyabet, glukoz, HbA1c, ölçüm belirsizliği

Introduction

Diabetes mellitus (DM), a disease characterized by high blood glucose levels, affects important organs such as the heart, blood vessels, eyes, kidneys, and nerves, causing complications such as kidney failure, blindness, lower extremity amputation, and cardiovascular diseases, and seriously affects the quality of life[1,2]. It is estimated that approximately 463 million individuals in the adult population aged 20-79 years worldwide in 2019 have diabetes, and this number is predicted to increase to 700 million in 2045. In this case, it is estimated that the proportion of diabetic patients will increase from 9.3% to 10.9%[3]. It has been suggested that diabetes and its complications cause 4.2 million deaths worldwide between the ages of 20 and 79, and approximately half of these (46.2%) are observed in people under 60 years of age[4].

According to the American Diabetes Association (ADA); each of the criteria for fasting plasma glucose ≥126 mg/dL, plasma glucose at 2nd hour of 75 g oral glucose tolerance test (OGTT) ≥200 mg/dL, HbA1c ≥6.5% [National Glycated Hemoglobin Standardization Program (NGSP) certified method] or random plasma glucose ≥200 mg/dL (In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis) alone is sufficient for the diagnosis of DM[5]. Medical laboratories are very important in the diagnosis of diseases and the follow-up of treatment. Because the precise accuracy of the test result may be limited, the concept of measurement uncertainty plays an extremely critical role in the evaluation process of test results. Measurement uncertainty is a statistical parameter that shows the quality of the analytical result and expresses the limits within which the measured value may vary. In this way, it provides the opportunity to evaluate the reliability of the measurement result. Knowing the level of uncertainty, especially in measurements at the border of medical decisions, is of great importance in the correct interpretation of test results and in providing valuable contributions to the treatment processes of patients[6].

In our study, it was aimed to calculate the measurement uncertainties of HbA1c and glucose parameters, which have important roles in the diagnosis and treatment of diabetes, and to evaluate the possible effects of these uncertainty values on clinical decision limits.

Materials and Methods

For our retrospective study, approval was obtained from the ethics committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital with the decision dated June 6, 2023, and numbered 2023/05-04. To calculate the measurement uncertainty, 6-months (July-December 2022) internal quality control (IQC) and 12-months (January-December 2022) external quality control (EQC) data of HbA1c and glucose tests were used.

EQC data of the tests were obtained from the External Quality Assurance Services (EQAS) (Bio-Rad Laboratories Inc., Irvine, CA, USA) quality control program. HbA1c levels were analyzed by ion exchange high-performance liquid chromatography (HPLC) method on the BIO-RAD Variant II instrument (Bio-Rad Laboratories, Marnes-la-Coquette, France), which was certified by the NGSP. The glucose test was measured by the hexokinase method using the AU5800 autoanalyzer device (Beckman Coulter Inc., CA, USA). The measurement uncertainty of HbA1c and glucose tests was calculated according to the ISO/TS 20914 uncertainty of measurement guide[7]. Desirable bias values were obtained from Westgard's biological database (www.westgard.com/biodatabase1.htm). Since the bias(%) values calculated from EQC data were lower than the desirable bias(%) values, they were not included in the uncertainty calculation.

Standard deviation (SD) of the IQC results was calculated. The SD was accepted as long-term precision (uRw). Calibrator uncertainty (Ucal) data was obtained from the manufacturer. The combined uncertainty calculation used the formula "$\sqrt{(URW^2 + UCAL^2)}$". Uncertainty calculations were made separately for both IQC levels. The expanded uncertainty was calculated by multiplying the combined uncertainty by coverage factor (The coverage factor was taken as 2 at the 95 confidence interval). The expanded uncertainty values were compared with the total allowable

error (TEa%) values of international organizations [Clinical Laboratory Improvement Amendments (CLIA) 2024, Desirable specifications for allowable total error, based on biological variability (BV), and rilibak][8-10].

In order to evaluate the possible effects of measurement uncertainty on clinical decision limits, the results of 31,030 patients who were requested simultaneous HbA1c and glucose tests in our hospital in 2022 were obtained from the hospital information management system. One hundred and sixty patients whose HbA1c and/or glucose test could not be studied due to preanalytical error (insufficient sample, clotted sample, inappropriate tube, etc.) were excluded from the evaluation. The HbA1c and glucose results of the patients were evaluated according to the ADA criteria, taking into account the measurement uncertainty, and the number of patients in the grey zone was determined.

Statistical Analysis

Data were analyzed using Microsoft Excel 2010, Statistical Package for Social Sciences (SPSS) version 25.0 software (IBM Corp., Armonk, USA), and MedCalc version 12 (MedCalc Software, Ostend, Belgium). In the statistical analyses, the chi-square test was used for categorical data. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results

Statistical values and measurement uncertainty of HbA1c and glucose tests are shown in Table 1. In our study, the measurement uncertainty values calculated of HbA1c and glucose tests were calculated as 2.41% and 7.92% for level 1 and 1.37% and 7.68% for level 2, respectively (Table 1). The uncertainty values calculated for the HbA1c parameter were below the TEa% values determined by all three international organizations. Although the uncertainty of the glucose test was below the CLIA and rilibak TEa% values, it was found to be higher than the BV TEa% value (Table 2).

The mean age of 30870 patients analysed retrospectively was 55±15 years, with HbA1c values between 3-18% and glucose values between 10-945 mg/dL. When the patients were evaluated according to ADA criteria, 9473 (30.7%) had prediabetes and 15557 (50.4%) had DM. Considering the HbA1c measurement uncertainty ±2.41% for level 1 and ±1.37% for level 2, the grey zones for level 1 and 2 in the DM cut-off value of 6.5% were between 6.3-6.7%, 6.4-6.6%, respectively (Figure 1). When the HbA1c results of the patients were evaluated according to the measurement uncertainty calculated for level 1 and level 2, it was seen that a total of 5309 and 3965 patients were in the gray zone and were affected by the uncertainty values, respectively (Table 3).

Considering the glucose parameter measurement uncertainty ±7.92% for level 1 and ±7.68% for level 2, the grey zone was between 116 and 136 mg/dL for the clinical decision limit for DM, which is 126 mg/dL (Figure 2). When glucose results were evaluated according to measurement uncertainty, 3959 (12.8%) patients were in the grey zone according to negative uncertainty and 5934 (19.2%) patients according to positive uncertainty. It was determined that the results of a total of 9893 patients were affected by uncertainty values (Table 3).

Table 1. Statistical values and measurement uncertainty of HbA1c and glucose tests

	IQC material	n	Mean	SD	U_{RW}^2	U_{CAL}	U_{CAL}^2	Combined uncertainty	Expanded uncertainty	Bias (%)	Desirable Bias(%)
HbA1c (%)	Level 1	100	5.2	0.08	0.01	1.20	1.44	1.20	2.41	0.25	1.5
	Level 2	100	10.2	0.15	0.02	0.67	0.45	0.69	1.37		
Glucose (mg/dL)	Level 1	145	98	3.43	11.76	1.98	3.93	3.96	7.92	-2.13	2.34
	Level 2	145	237	3.29	10.82	1.98	3.93	3.84	7.68		

IQC: Internal quality control, SD: Standard deviation, U_{RW}: Long-term precision, U_{CAL}: Calibrator uncertainty

Table 2. The measurement uncertainty of the parameters and TEa values of international organizations

	Level 1 measurement uncertainty	Level 2 measurement uncertainty	CLIA TEa%	BV TEa%	Rilibak TEa%
HbA1c	2.41	1.37	8	3.0	18
Glucose	7.92	7.68	8	6.96	15

CLIA: Clinical Laboratory Improvement Amendments, BV: Desirable specifications for allowable total error, based on biological variability, TEa: Total allowable error

Table 3. The effect of measurement uncertainty of HbA1c and glucose tests on diagnostic performances in the diagnosis of DM

Test		Cut-off value		DM		PPV (%)	NPV (%)	Sensitivity % (95% CI)	Specificity % (95% CI)
				Negative	Positive				
HbA1c	Level 1	6.5%	Negative	15313	1357	100	91.9	91.3 (90.8-91.7)	100 (100-100)
			Positive	0	14200				
		6.3%	Negative	13817	997	90.7	93.3	93.6 (93.2-94.0)	90.2 (89.7-90.7)
			Positive	1496	14560				
		6.7%	Negative	15313	2816	100	84.5	81.9 (81.3-82.5)	100 (100-100)
			Positive	0	12741				
	Level 2	6.5%	Negative	15313	1357	100	91.9	91.3 (90.8-91.7)	100 (100-100)
			Positive	0	14200				
		6.4%	Negative	14638	1170	95.5	92.6	92.5 (92.1-92.9)	95.6 (95.3-95.9)
			Positive	675	14387				
		6.6%	Negative	15313	2120	100	87.8	86.4 (85.8-86.9)	100 (100-100)
			Positive	0	13437				
Glucose	Level 1&2	126 mg/dL	Negative	15313	4162	100	78.6	73.2 (72.5-73.9)	100 (100-100)
			Positive	0	11395				
		116 mg/dL	Negative	14236	2882	92.2	83.2	81.5 (80.9-82.1)	93.0 (92.6-93.4)
			Positive	1077	12675				
		136 mg/dL	Negative	15313	5934	100	72.1	61.9 (61.1-62.6)	100 (100-100)
			Positive	0	9623				

DM: Diabetes mellitus, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

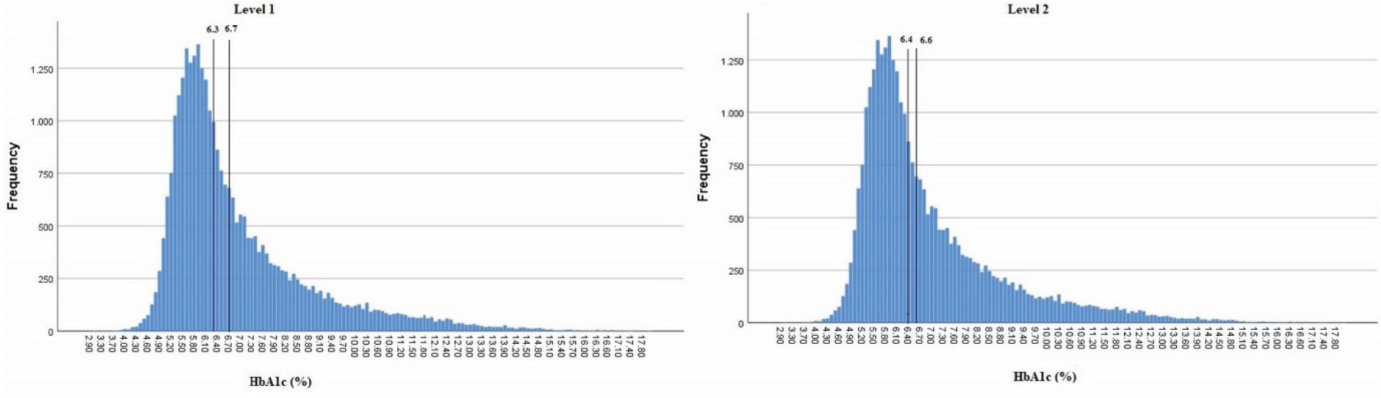

Figure 1. HbA1c values in the gray zone according to level 1 and level 2 measurement uncertainty

Discussion

Measurement uncertainty is a statistical parameter that evaluates the reliability and accuracy of the measurement result obtained. This parameter refers to the range containing the value of the measured quantity and quantitatively indicates the quality of the result. The measurement uncertainty is reported together with the measurement result, showing a distribution that is reasonably consistent with the value of the measured quantity. In this way, it provides information about the reliability and precision of the measurement result[11]. In our study, the measurement uncertainty values of HbA1c and glucose tests were 2.41% and 7.92% for level 1 and 1.37% and 7.68% for level 2 at 95% confidence interval, respectively. In our laboratory,

uncertainty values calculated for the HbA1c parameter were below the TEa% values determined by all three international organizations. Although the uncertainty of the glucose test was below the CLIA and rilibak TEa% values, it was found to be higher than the BV TEa% value. Even at these measurement uncertainty values, which are within acceptable limits for the clinical biochemistry laboratory, 12629 false negative results and 2573 false positive results were found for level 1 uncertainty, and 12106 false negative results and 1752 false positive results were found for level 2 uncertainty. Considering that the number of patients in the grey zone will increase as the measurement uncertainty value increases, the quality and reliability of the results are very important.

In the study of Dülgeroğlu[6] the expanded measurement uncertainty of HbA1c measured by the cation exchange chromatography method in the BIO-RAD D10 HPLC device was found to be 7.4%. It has been reported that there is a measurement uncertainty of ±0.4% for HbA1c at the level of 6% and it may affect the clinical decision[6].

In the study of Ayyildiz and Kalayci[12] the measurement uncertainty of HbA1c on the Trinity Biotech Premier Hb9210 device was found to be ±4.27% at 95% confidence interval, which is lower than the total allowable error determined by international organisations (clia, rilibak, Fraser rules). It was reported that the HbA1c threshold value of 6.5% had a measurement uncertainty between 6.2% and 6.8% and 1539 (11.5%) of 13329 patients had HbA1c results in the grey zone. Since the uncertainty value of each laboratory is different from each other, it has been suggested that the grey zones of parameters evaluated using cut-offs such as HbA1c should be determined according to the measurement uncertainty[12].

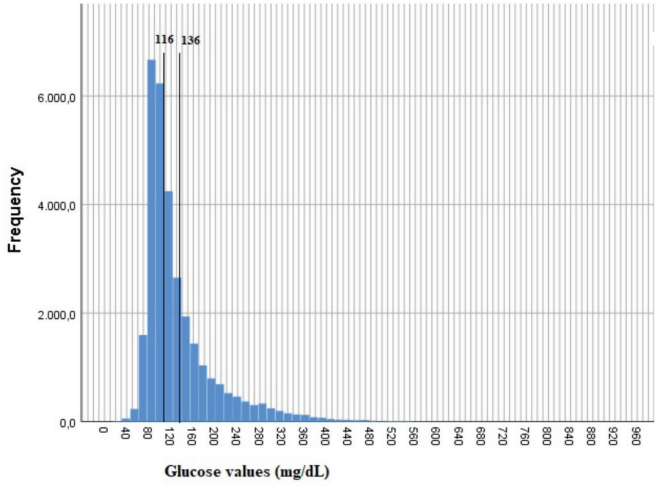

Figure 2. Glucose values in the grey zone

In the study of Unal and Atikeler[13] the measurement uncertainty (95% confidence interval) of HbA1c on the Trinity Biotech Premier Hb9210 device was calculated as ±4.6%. It was observed that the results of 1555 (15.2%) patients with HbA1c values between 6.2-6.8% were affected by the uncertainty value[13]. In the study by Galindo-Méndez et al.[14], HbA1c measurement uncertainty values were found to be significantly different from each other, ±0.19% and ±0.43%, respectively, due to different bias results obtained using two different EQC programmes (Unity Interlaboratory Programme and Randox International Quality Assessment Scheme). However, in both cases, the measurement uncertainty results were reported to be below the recommended maximum uncertainty of ±0.5%[14].

In the study by İnce et al.[15], the measurement uncertainty of the glucose parameter in the Abbott/Architect C8000 autoanalyser was found to be 3%. It has been suggested that the uncertainty value for the 126 mg/dL limit used in the diagnosis of diabetes is ±3.78 mg/dL and all error sources that may affect the result should be identified and given as uncertainty value[15]. In the study of Telo and Kaman[16] the measurement uncertainty of the glucose test performed on the Siemens Advia 2400 autoanalyser was similarly found to be 3.9%. In the study of Bal et al.[17], the measurement uncertainties of glucose parameters in three different devices of the same brand and model (DxC 800, Beckman Coulter) were found to be 3.22%, 5.81% and 3.74%, respectively. Celebiler et al.[18] reported the measurement uncertainty for glucose in the Roche/Hitachi Modular P800 autoanalyser as ±6% in the 95% confidence interval.

In the study of Öztürk et al.[19], investigating the effect of glucose measurement uncertainty in the diagnosis of gestational diabetes, 150 of 937 pregnant women had a 1st-hour glucose result ≥140 after 50 g OGTT. Sixty-six of these pregnant women were diagnosed with gestational diabetes after 100 g OGTT. The uncertainty of the glucose test performed on the Olympus AU2700 autoanalyzer was found to be 7.26% and it was reported that 77 patients were diagnosed with gestational diabetes according to negative uncertainty and 55 patients were diagnosed with gestational diabetes according to positive uncertainty[19]. In the study by Kütükçü et al.[20], investigating the importance of the use of measurement uncertainty and reference change value in the

diagnostic evaluation of biochemical tests, the measurement uncertainty of glucose was found to be 5.39 and 4.30 in Architect ci4100 and ci8200 devices, respectively. They stated that measurement uncertainty and reference change value should be given together with the test results to increase diagnostic accuracy[20].

In the study conducted by Çat and Uçar[21] in 2023, the measurement uncertainty of the glucose test was calculated separately for two levels of IQC in the same brand and model A and B devices (Roche Cobas 6000 c501). The uncertainty of glucose was found to be 5.3% and 3.8% for IQC-1 and 2 in device A and 13.7% and 4.4% in device B, respectively. It was noted that the calculated measurement uncertainty for IQC-2 in both instruments met the targeted quality specification (5%) but exceeded the permissible targets for IQC-1. It has been reported that different measurement uncertainty values can be obtained for the same analyte in different materials and different instruments[21].

Study Limitations

One of the strengths of our study is that it is the first study to simultaneously calculate the measurement uncertainty of HbA1c and glucose parameters, which have an important place in the diagnosis and treatment of DM, according to the ISO/TS 20914 guideline. The second is to evaluate the effect of measurement uncertainty in HbA1c and glucose tests on diagnostic performance in a large patient group.

Conclusion

Although the measurement uncertainty values of HbA1c and glucose tests in our laboratory are within acceptable limits, it has been observed that false negative and false positive results may occur. However, when glucose and HbA1c results at medical decision levels are evaluated together with measurement uncertainty, diagnosis and treatment modality may change. It should be taken into consideration that false negative results may lead to delay in diagnosis and related complications, while false positive results may cause unnecessary test and treatment costs.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital with the decision dated June 6, 2023, and numbered 2023/05-04.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: M.A., Design: M.A., Data Collection or Processing: M.A., F.D., Analysis or Interpretation: M.A., F.D., Literature Search: M.A., F.D., Writing: M.A., F.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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