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Research Article

Validation study of Hba1c kit to be used in diabetic population

Diyabetik nüfus taramasinda kullanilacak Hba1c kiti doğrulama çalişmasi

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Abstract

Aim: A validation study of the HbA1c kit to be used in screening patients diagnosed with Diabetes Mellitus admitted to the hospital.

Material and Methods: In addition to the internal and external controls of the HbA1c kit used in routine analyses, in-laboratory verification and validation studies, validation steps of the test, accuracy (precision), and report range were carried out.

Result: All steps of the verification and validation of the HbA1c kit have been carried out and recorded in the hospital medical laboratory. Inter-study reproducibility (%CV) 0.88, Method / reference material comparison (% Bias) 3.94 Target: (% Bias + 1.65 (%CV) < TEa) As a result, TAH: 5.40 < TEa: 18 (rilibak) was calculated and The kit has been verified.The accuracy of the kit to be used in diabetic population screening is important as it will affect the clinician's prediction in the treatment and follow-up of a costly and common disease. All laboratories, whether commercial kit or not, should carry out verification procedures in order to increase laboratory reliability and quality. It should be mandatory to provide the right direction to clinicians, especially in the analysis of diseases that will affect society. Adding the validation data of the kit to the research data, which will be used in long-term studies that will affect a large population, will also increase the effectiveness of the study.

Keywords: Validation; Verification; Measurement Uncertainty; Truth; Precision; Diabetes Mellitus; HbA1c

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Öz

Amaç: Hastaneye başvuran Diyabetes Mellitüs tanılı hastalarda taramada kullanılacak olan HbA1c kiti doğrulama çalışması

Gereç ve Yöntemler: Rutin analizlerde kullanılan HbA1c kiti internal ve external kontrolleri yanısıra laboratuvar içi doğrulama validasyon çalışmaları testin geçerli kılma basamakları, doğruluk (accuracy) Kesinlik (presizyon) ve rapor aralığı işlemleri yapılmıştır.

Sonuç: Hastane tıbbi laboratuvarında HbA1c kitinin bu doğrulama ve geçerli kılma işlemlerini tüm basamakları yapılmış ve kayıt altına alınmıştır. Çalışmalar arası tekrarlanabilirlik (%CV) 0.88, Yöntem / referans materyali karşılaştırma (% Bias) 3.94 Hedef: (% Bias + 1.65 (%CV) < TEa) Sonuç olarak TAH:5,40< TEa:18 (rilibak) olarak hesaplanmıştır ve kit verifiye olmuştur. Diyabetik popülasyon taramasında kullanılacak olan kitin doğruluğu maliyetli ve yaygın bir hastalığın tedavi ve takibinde klinisyen öngörüsünü etkileyeceği için önemlidir.Tüm laboratuvarlar ticari kit olsun olmasın doğrulama işlemlerini laboratuvar güvenirliğini ve kalitesini artırmak adına yapmalıdır. Özellikle toplumu etkileyecek hastalıkların analizlerinde klinisyenlere doğru yön vermek adına yapılması zorunlu olmalıdır. Geniş popülasyonu etkileyecek uzun süreli çalışmalarda kullanılacak kitin doğrulama verilerinin araştırma verilerine eklenmesi de çalışmanın etkinliğini artıracaktır.

Anahtar kelimeler: Validasyon; verifikasyon; ölçüm belirsizliği; doğruluk; kesinlik; Diyabetes Mellitüs; HbA1c

Introduction

Verification and validation are two of the most confusing definitions. Verification is the process of error evaluation. In other words, validation focuses on analytical errors. The types of errors and how to identify these errors, what analytical procedures will be applied and how much data will be needed, what statistical procedures should be applied, and what the tolerable error size will be are included in the validation process. Validation is the process of proving that a process, system, equipment or method operates as expected and meets its intended use in the CLSI and ISO Definitions. Verification is defined as "the process of verifying by examining and obtaining positive evidence that shows that the specified goals have been achieved" [1, 2, 3].

Our hospital applied for TUSKA (Turkish Health Services Quality and Accreditation Institute) hospital accreditation in 2018. Among the accreditation laboratory criteria, method validation has been carried out in the ready-made commercial kits used in the laboratory within the scope of the criterion "SH.LH.04.03, validation/verification studies and continuous quality control procedures should be carried out for the reliability of test results" in the accreditation standards application guide in health[4].

The hospital has been holding the HIMSS level 7 full digital hospital certificate since 2016[5]. It has been revalidated 3 times since 2016 and has been validated. During this process, clinical decision support systems that provide added value to the physician and the laboratory, made with clinical units in a fully digital structure, and laboratory-clinical applications have been made within hospital information systems[6].

In the HIMSS-EMRAM validation processes, application examples regarding financial, temporal, service quality and reliability in the healthcare service provided by using the digital structure were presented to the HIMSS-EUROPA audit team as analysis. In these analyses, an in-laboratory validation study of the HbA1c commercial kit was conducted for a long-term study on patients diagnosed with diabetes who were admitted to the hospital and whose HbA1c value was 9.

Our hospital has carried out in-laboratory kit validation studies in accordance with 1 international (HIMSS-EMRAM) and 1 international (TUSKA) standards. The example here is the commercial kit validation study that will be used to screen patients with HbA1c values of 9 and above in patients admitted to the hospital after the digital structuring in HIMSS-EMRAM Standards.

Ready-made commercial kits are used in routine studies in most medical and non-medical laboratories globally. Although these kit methods are used, each laboratory must verify the performance of the testing system before reporting its results. Almost all of the test parameters used in hospital medical laboratories are ready-made commercial kits.

It means objective testing and written documentation of the suitability of the stages of a measurement for specified purposes. These are testing and measurement processes performed to determine the performance of a method. The method varies depending on multifactorial interactions.

(Laboratory conditions, device, chemical substance used, standard, operator experience, etc.) Each laboratory must determine the performance of the test and analysis results performed with the method under its own conditions[7].

Under what circumstances would method validation be needed:

When any method will be applied for the first time in a laboratory, when a change is made in the method being used, when a validated method will be used in another laboratory or when measurements will be made with a different person or a different device, if there is a change at the end of the control tests, a validation study of the test will be carried out before a new research. There is an indication.

In ISO 22000:2018, verification is defined as providing evidence that the specified conditions are met (8).

For the validity of a test to be used in the laboratory, the following must be done.

To confirm that the necessary conditions for the specific purpose are met after the examination and to provide evidence. Validation/verification studies must be carried out before a new method is put into routine use. These verification procedures need to be performed repeatedly in some cases.

There are many device changes, especially in medical laboratories where ready-made commercial kits are used, as there are kit tenders. For devices with frequent device changes, validation and verification should be carried out in case of changes in the basic chemicals for which the kits are prepared by the laboratory (in case of method change), personnel, or in cases where the method will be used. First time for any changes in the laboratory that could affect the results All laboratory branches play an active role in diseases and their accurate diagnosis, risk factors, and effective prophylactic and treatment of diseases. To achieve this role, effective implementation of a quality system is essential in every laboratory seeking accreditation [7]. Worldwide validity can be met by providing accreditation to ISO/IEC 17025 for testing and calibration laboratories and ISO 15189 for medical laboratories. It covers the managerial and technical capabilities of a laboratory. The hallmark of the accreditation process is method validation, verification and quality assurance[8,9].

Some definitions cover some calculations in procedures.

Accuracy: Deviation of the measured value from the calibrated value or true value.

Precision: The ability to obtain close values of measurement obtained by repeating with the same sample.

Precision: It is also the degree of closeness of the values of independent measurements under certain conditions. Uncertainty calculations were replaced by repeatability and reproducibility definitions. The definition of precision is defined as repeatability and reproducibility.

Measurement uncertainty: The parameter characterizing the distribution of values that accompany the measurement result and that can reasonably correspond to the quantity measured. It is also referred to as "the parameter associated with the measurement that defines the distribution of values associated with the measured quantity". In this regard, k=2 is taken for a Confidence Interval of approximately 95%.

Bias: The difference between the average measured value and the accepted value (i.e., the certified or nominal value) obtained from a large number of measurements. The concept of reality is expressed with bias

Accuracy and precision must be in accordance with the reference ranges given by the manufacturer and the patient population of the laboratory. For this purpose, method comparison must be performed to detect bias or inaccuracy, repetition studies must be performed to detect impression, linearity studies must be performed to determine the report range, and a review of reference values must be performed to verify the reference range[9-10,11].

For a test to be validated, the laboratory manager must perform and record these steps and document the conformity of the reference values in the manufacturer's prospectuses and books.

Material and Methods

The HbA1c Kit, which is a CE-approved ready-made commercial kit, was used in the hospital medical biochemistry laboratory as a qualitative measurement kit and its characteristics are stated in the "Method Approval Evaluation Form". The information is taken from the company kit prospectus. The validation for the HbA1c kit in our Hospital Medical Laboratory was planned and performed as follows. All data were recorded.

1. Level 2 Internal Quality Control Material was used as the reference material for intra-study repeatability. These data were recorded in the device memory as of 30.10.2022.

2. The % CV values taken when calculating the total error were calculated by using accuracy and inter-study reproducibility data. Internal quality control material was used as reference material. % CV is the absolute average of Level 1 and Level 2 studies. The values taken for these data are available on the Daily Internal Quality Control Screen between 16.10.2022 and 27.10.2022.

3. BIAS values were determined by taking the absolute average of the accepted and valid bias values of the 2022 external quality studies. The invalid and unacceptable values were removed.

4. Total Error (TE) was calculated with the following formula

%TAH=%CV X 1.65 + BIAS

These values were compared with the Total Acceptable Error (TAE) values published by international reference organizations (BV DESIRABLE, CLIA, RILIBAK, IPH BELGIUM, BV MINUMUM, RCPA, CFX, AAB) and the values that met the following equation

%TE<% TAE were verified for our laboratory.

5. Measurement uncertainty calculation was made by taking twice the absolute average of the reproducibility of Level 1 and Level 2 %CVs in studies

(ABSOLUTE (Level 1 %CV + Level 2 %CV)) / 2) X 2).

Expanded measurement uncertainty was used and the k value was taken as 2.

6. The test principle, sample type, reference range, analytical measurement range, clinical reportable range, analytical sensitivity, and interference data in the Method Approval Data Form were taken from the package inserts sent by the companies with the kits.

7. When controls with new lot numbers and different values are entered into the system (i.e., internal quality control screen), the system changes all the values in a retrospective fashion. For this reason, target values between studies and within studies do not match.

8. The documents used in the study are as follows.

a. Method Approval Data Form (Quantitative tests) x 2

b. Method Approval Evaluation Form

c. External quality BIAS values, our laboratory's TE and international TAE values table

d. Measurement Uncertainty Table

Results

Table 1. Within-run repeatability

Control Number	Target value	Mean	SD	CV%
Control 1	5.58	4.885	0.05275	1.0799
Control 2	9.35	9.369	0.08425	0.8999

Table 2. Inter-study reproducibility

Control Number	Target value	Mean	SD	CV%	% Bias
Control 1	5.58	5,607	0.06272	1.1187	-0,4839
Control 2	9.35	9.422	0,0619	0.6577	-0,7701

Table 3. Test verification final calculations

Within-run repeatability (% CV)	0.98
Inter-study reproducibility (%CV)	0.88
Method/Reference material comparison (% Bias)	3.94
TARGET: % Bias + 1.65 (%CV) < TEa	TAH:5,40< TEa:18 (rilibak)

Discussion

Some branches are indispensable for all clinicians, supporting diagnosis and guiding follow-up and treatment. Getting accurate data from these branches is very important in charting a path for self-diagnosis and follow-up.

Ready-made commercial kits are used in medical laboratories on a global scale. Although internal quality and external quality controls are used, laboratories can perform the validation and verification processes to control their own accurate measurement and reliability.

Like any other tests, the HbA1c ready-made commercial kit is regularly checked externally and internally and evaluated by laboratory specialists in the hospital medical laboratory. However, this is not sufficient for the reliability of the test. Validation and verification procedures must be performed for the test the laboratory will use.

Documenting the accuracy of a test to be performed before a study is conducted for the diagnosis and follow-up of a disease that is costly for the demographic structure of the entire society and the country is very important in evaluating the study data [12].

Complications such as retinopathy, neuropathy, and nephropathy may occur because of high blood sugar levels in diabetic patients. The multitude of complications is the reason for referral and examination to all branches. For this reason, early diagnosis and diabetes control reduces the relevant costs [13 (1),14].

This test provides benefits in many areas such as investigating the complications that are associated with high blood sugar levels, determining risk factors, and adjusting the insulin dose accordingly.The HbA1c Test is a common blood test used to diagnose and monitor Type 1 and Type 2 Diabetes. HbA1c Test means glycated hemoglobin, glucose-bound hemoglobin. HbA1c, but by internationally standardized methods

When measured, it can be used as a diagnostic test. In our country

Since HbA1c measurement tests have not been standardized yet, only

It is not recommended to be used as a diagnostic test on its own. In the presence of anemia, hemoglobinopathies, pregnancy (2nd and 3rd trimester), which affect some HbA1c

tests, patients who use antioxidants such as vitamins C and E should be excluded from the screening[16].

The HbA1c Test result shows the average blood sugar level over the last 3 months and measures how much erythrocytes are exposed to glucose and what percentage of the oxygen-carrying protein hemoglobin is bound to glucose.

Diabetes Mellitus is a very expensive disease, both in treatment and follow-up, due to multiorgan involvement in all countries and societies. Protective preventive actions become important in this disease, as it affects every branch due to complications. Chronic hyperglycemia causes long-term complications such as retinopathy, neuropathy, and nephropathy[17].

It often accelerates macro and micro vascular changes. Sedentary lifestyles around the world have made diabetes a global epidemic, and approximately 346 million people have been diagnosed with diabetes worldwide. In the cost analysis conducted in the USA, diabetes-related expenses constitute 1 out of every 7 dollars in the health budget [18,19].

Efficient and effective management is required to overcome this epidemic. Portable glucose meters facilitate short-term management of diabetes. Long-term prospective studies, particularly the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study Group (UKPDS) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, have provided conclusive evidence that diabetic complications are directly associated with diabetes. It refers to the glycemia value measured by HbA1c concentration

These types of disease groups, which affect large masses and whose treatment and follow-up are costly in terms of time and money, are important to guide clinicians. For this reason, the kit to be used in the analysis to be carried out in studies covering a long period of time and a large population must be validated, whether it is created under commercial or laboratory conditions. and its inclusion in the research would be more accurate in clinicians' approach to the disease.

Conclusion

In our hospital laboratory, validation, and verification studies were performed before the HbA1C screening study was planned together with public health. When the process steps were evaluated, the accuracy, precision, measurement range, and reference range of the method used were confirmed by our studies. Method validity was documented by meeting the abovementioned criteria

All laboratories must conduct pre-study validation studies and certify that the method is valid on their behalf, whether commercial or not. Internationally accredited laboratories around the world are indispensable analysis sources for all clinical branches and are used as references for every critical disease group. Every laboratory specialist aims to be in this group of laboratories.

The present study is a kit validation study conducted within the laboratory to verify whether the commercial kit purchased works correctly or not. For this reason, it is not included in the criteria requiring an ethics committee.

There is no institution or organization that financially supports the study.

Conflict of Interest

There is no conflict of interest

Ethics Committee

I hereby declare that, in accordance with the Personal Data Protection Law, retrospective studies are not among the studies that require an ethics committee and that they are not required.

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