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The estimation of uncertainty of measurement of glycated hemoglobin as an analytical performance specification and in the interpretation of its results

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A B S T R A C T

Background: Glycated hemoglobin (HbA1c) plays a key role in monitoring the glycemic state of an individual. Uncertainty of measurement (*U*) indicates the magnitude of the doubt about a measurement result. To properly classify an individual as under either good or poor glycemic control, it has been suggested that *U* of an HbA1c result should not exceed ± 0.5%.

Methods: The statistical method used to calculate uncertainty of measurement was the "top down" approach suggested by EURACHEM/CITAC. This approach allows the inclusion of imprecision, bias, uncertainty of bias and uncertainty of the calibration of the HbA1c method. The value of bias was obtained using data generated from the external quality assessment of the Randox International Quality Assessment Scheme and that of the Unity data management software system. Imprecision was calculated after the daily analysis of two levels of control sera.

Results: Calculation of uncertainty of measurement of HbA1c was a straightforward procedure used to calculate *U*. Due to the different bias results obtained using two different external quality programs, the results of *U* were significantly different (± 0.19% vs ± 0.43%) from each other; however, in both cases, the *U* results were below the maximal suggested uncertainty of ± 0.5%.

Conclusions: The calculation of *U* of HbA1c by the EURACHEM/CITAC method is a practical approach that can be used as an additional analytical goal in the measurement of HbA1c. In addition, this information can aid clinicians to determine the level of confidence that can be placed in the test results.

1. Introduction

Diabetes is a chronic, degenerative disease responsible for micro and macrovascular complications such as retinopathy, nephropathy, arterial disease, that may lead to infarction, stroke and amputations. According to the World Health Organization, there are over 420 million people worldwide living with diabetes, with the global prevalence (age-standardized) doubling since 1980, rising from 4.7% to 8.5% in the adult population. In addition, diabetes is directly responsible for over 1.5 million deaths a year [1].

The proper glycemic control of the diabetic patient is a key component in the global strategy to reduce the complications and deaths related to diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) have shown a direct relation between good glycemic control, measured by the blood concentration of glycated hemoglobin (HbA1c), and the reduction of the overall risk of developing diabetes complications [2,3].

Due to the high impact that the HbA1c results generated by clinical laboratories have on the monitoring of diabetic patients and, in the last few years, in the diagnosis of diabetes, it is the responsibility of every clinical laboratory to continuously monitor the performance of their methods, assuring that these methods achieve the proper analytical performance specifications to guarantee that their results are fit for their clinical purpose.

One of the most employed parameters in the field of metrology, used to determine the level of confidence placed on a given result, is uncertainty of measurement (*U*), that is defined as "the non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used" [4]; in other words, it is the interval associated with a certain probability in which the true results lies [5]. In the case of the clinical laboratory, *U* could be used for three purposes: first, to guarantee that the results are fit for their clinical purpose; second, to help the users with the interpretation of these results and third, to comply with ISO 15189 accreditation requirements.

There are currently several different approaches for *U* estimation; however, as suggested by Jones [5], a "one size fits all" calculation of *U* in the clinical laboratory is not advisable, as the method of choice should depend on whether the test result will be compared (1) with previous results from the same patient or the references values established for the analyte or (2) with established clinical decision limits, where multiple measurements procedures are used. When *U* is used in the first scenarios, bias becomes irrelevant in the calculation of this parameter, and all the uncertainty of the test results lies on the precision of the method; however, in the latter scenario, such as is the case of HbA1c, where the analyte has reference measurement procedures with

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calibration of routine methods traceable to primary reference materials, bias should be considered in the calculation of uncertainty of measurement [6].

The objective of this study was to demonstrate the calculation of uncertainty of measurement of glycated hemoglobin by following the method proposed by EURACHEM/CITAC [7], suggesting the adoption of this parameter as an analytical performance specification used by clinical laboratories as part of their quality control to guarantee the accuracy of their HbA1c results. Additionally, we suggest to include in the final HbA1c reports the result of *U* of the laboratory, so clinicians can determine with a stated level of confidence the interval where the true level of the glycemic control of the patient lies.

2. Materials and methods

The calculations for the uncertainty of measurement for this study were performed by the data generated from the internal and external quality control of a private Mexican clinical laboratory (Laboratorios Galindo SC, Oaxaca, Mexico) in the time period from October 2017 to March 2018. HbA1c is routinely measured on the D-10 analyzer (Bio-Rad Laboratories Inc., USA). Calibration of the instrument is performed according to the manufacturer's instructions and must be done at least once per cartridge; thus, multiple calibrations were performed during the time of the study period.

The statistical method used to obtain the uncertainty of measurement of HbA1c was the "top down" approach, previously described in the EURACHEM/CITAC guide [7]. This approach allows clinical laboratories to calculate the uncertainty of the results generated from the quality control data of the laboratory, using the following general formula:

$$u_c = (u_{(Rw)}{}^2 + u_{(Bias)}{}^2)^{1/2}$$

where the uncertainty component associated with possible random errors, $u_{(Rw)}$, and that associated with possible systematic errors, $u_{(Bias)}$ are calculated separately. The minimum required fields in evaluating measurement of uncertainty using the "top-down" approach are identifiable from the following steps:

1. Define the measurand, which is the quantity intended to be measured.
2. Identify the sources of uncertainty. For the calculation of uncertainty, only its analytical sources were considered, including that associated with random errors, $u_{(Rw)}$, as well as that associated with systematic errors, $u_{(Bias)}$. As it is currently extremely difficult to include the non-analytical uncertainty of the test result in the estimation of *U*, the risk of errors in these phases are decreased to a minimum following the organization's accredited quality management systems based on ISO 15189:2012.
   - 2.1 The uncertainty associated with random errors was obtained from the daily analysis of the same batch of two levels (I and II) of Lyphochek Diabetes Controls (Bio-Rad Laboratories Inc., USA), with an HbA1c concentration of 5.4 (36 mmol/mol) and 9.6% (81mmol/mol), respectively.
   - 2.2 The uncertainty associated with systematic errors was obtained from two different sources: (a) the calculation of bias of the laboratory's results compared to those of other laboratories (peer group) participating in the Unity Interlaboratory Program (Bio Rad Laboratories Inc., USA) and (b) to those participating in the Randox International Quality Assessment Scheme (RIQAS, UK). Our results were compared to those of our peer group rather that to all-methods results because, even in harmonized and standardize analytes such as glycated hemoglobin, "PT/EQA surveys show significant biases between method subgroups" [8]. The uncertainty calculation associated with systematic of errors, $u_{(Bias)}$, was obtained following the next steps:
     - 2.2.1 Calculate the monthly bias of the laboratory from the external quality assessment programs (Bias);
     - 2.2.2 Calculate the mean square value of the monthly bias results of the laboratory by $RMS_{Bias} = (\Sigma\ (Bias^2)\ /\ n)^{1/2}$;
     - 2.2.3 Independently, calculate the uncertainty of the reference value, $RMS(u_{(Cref)})$, of both the Unity and RIQAS programs by $RMSu_{(Cref)} = 1.25 \times (CV_{group}\ /\ (n_{\ peer\ group})^{1/2})$;
     - 2.2.4 Calculate the uncertainty associated to bias by $u_{(Bias)} = (RMS_{Bias}{}^2 + RMS_{u(Cref)}{}^2)^{1/2}$
3. Quantify the combined standard uncertainty, $u_{(c)}$
4. Calculate the expanded uncertainty, *U*, including a coverage factor of $K = 2$, which provides an expanded uncertainty at approximately the 95% confidence level. With the objective of including the largest possible number of variables that influence the uncertainty of our method, the uncertainty of the calibrators of our instrument of measurement was incorporated as the mean square value of this uncertainty plus *U*.

The analytical performance specification of the uncertainty of measurement established for the present study was that previously suggested of below ± 0.5% of the HbA1c result [9,10]. The units of the concentration of HbA1c chosen for this study were the percentage (%) of glycated hemoglobin in relation to the concentration of total hemoglobin, as suggested by National Glycohemoglobin Standarization Program (NGSP), over those of mmol/mol suggested by the International Federation of Clinical Chemistry (IFCC), as the use of the former is, by far, more common in Mexico.

3. Results

The results and calculation of the uncertainty of measurement of HbA1c during the study period are outlined below, including each of the criteria suggested by EURACHEM/CITAC.

1. Define the measurand

HbA1c is defined as the concentration in whole blood extracted in EDTA tubes of hemoglobin molecules having a special hexapeptide in common, which is the stable adduct of glucose to the N-terminal valine of the hemoglobin β-chain.

2. Identify the sources of uncertainty (For the calculation of the uncertainty of measurement of our study, only its analytical sources were considered).

- Volume of samples and reagents
- Batch-to-batch variation of reagents and calibrators
- Spectrophotometric measurement
- Sample stability
- Method linearity
- Analyst

2.1 Calculate the HbA1c method imprecision (Coeficient of variation – CV%)

The results of the laboratory imprecision obtained during the time period of the study are shown in Table 1.

Based on the American Diabetes Association (ADA) quality control criteria [10], the imprecision results obtained fulfill the recommended analytical performance specifications of CV ≤2.0% in both of the controls analyzed.

2.2 Calculate the HbA1c method bias

The results of our method bias (RMS_{Bias}), obtained during the time period of the study are shown in Tables 2 and 3; those of the

Table 1
Imprecision results of control sera I and II.

	Control I	Control II
HbA1c expected concentration as indicated by provider (Lyphochek Diabetes Controls)	5.40%	9.60%
Number of results analyzed	151	151
Laboratory mean concentration of results	5.38%	9.84%
Laboratory mean CV	1.10%	0.80%

Table 2
Bias results of controls I and II using the *Unity* data management software system.

	Control I	Control II
HbA1c expected concentration as indicated by provider (Lyphochek Diabetes Controls) %	5.40%	9.60%
Monthly average of participants in the peer group	3699	4670
Mean concentration of peer group	5.41%	9.80%
CV of peer group	2.90%	2.50%
Laboratory RMS_{Bias}	1.28%	0.87%

Table 3
Bias results using the external quality assessment program RIQAS.

	Results
Monthly average of participants in the peer group	105
Coefficient of variation of the peer group	2.10%
HbA1c mean concentration of all methods	7.72%
HbA1c mean concentration of the peer group	7.80%
HbA1c mean concentration of the laboratory	7.70%
Laboratory RMS_{Bias}	1.70%

Table 4
Results of the expanded uncertainty obtained from the Unity Interlaboratory Program and the *Randox International Quality Assessment Scheme (RIQAS)*.

Parameter	Unity interlaboratory program		RIQAS	
	Control I	Control II	Control I	Control II
HbA1c expected concentration as indicated by provider (Lyphochek Diabetes Controls) %	5.40	9.60	5.40	9.60
RMS_{Bias} %	1.28	0.87	1.70	
$RMSu_{(Cref)}$ %	0.20	0.12	0.30	
$u_{(Bias)}$ %	1.30	0.88	1.73	
$u_{(c)}$ %	1.70	1.19	2.05	1.91
U %	3.40	2.38	4.10	3.82
Calibrator uncertainty %	Level I 1.60 Level II 1.00 Combined calibrator uncertainty 1.89			
U % (Including calibrator uncertainty)	3.89	3.04	4.51	4.26
Uncertainty of measurement in the HbA1c concentration of the control	± 0.21	± 0.16	± 0.44	± 0.42
Uncertainty of measurement in the HbA1c concentration between 5.40 y 9.60%	± 0.19		± 0.43	

uncertainty associated with bias, $RMSu_{(Cref)}$, in Table 4.

2.3 Quantify the combined standard uncertainty, $u_{(c)}$ and the expanded uncertainty, *U*.

The results of $u_{(c)}$ and *U*, including the uncertainty associated with the instrument's calibration, generated by the calculations obtained from the internal quality data (Unity system) and those obtained from an external scheme (RIQAS) are shown in Table 4.

4. Discussion

Due to the importance that the measuring of the HbA1c concentration in whole blood plays in the proper control of a diabetic patient, organizations such as the IFCC and NGSP have implemented different actions aimed at standardizing this measurand. However, independently of these efforts, it is the responsibility of each clinical laboratory to assure that its HbA1c results achieve the proper analytical performance goals to guarantee that they are fit for their clinical purpose.

Different studies have shown that the highest hierarchy of analytical performance specifications in the determination of HbA1c, as indicated by the Milan consensus suggested by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), can be achieved by clinical laboratories. Such specifications include a coefficient of variation in the daily analysis of the laboratory's internal quality control of $< 2\%$ and a maximum allowable total error (TE) of 6.7% [9–11]. The limitations of these quality goals is that the former only takes into consideration the precision component of the analytical process, not including bias, and the latter includes the possibility of an acceptable TE that may include the unacceptable performance of one of its components (bias or imprecision). Additionally, neither analytical specification takes into consideration the uncertainty associated with determining bias, thus providing additional uncertainty as to the true value of the measurand, and both quality goals are of little use to the clinician in helping in the interpretation of the test results.

Uncertainty of measurement is a parameter widely used in different fields of metrology; however, its use in the clinical laboratory is not widespread. According to ISO/IEC 17025, “General requirements for the competence of testing and calibration laboratories”, the estimate of the uncertainty of measurement should be included in test reports when it is relevant to the validity or application of the test results [12]. Under this premise, in this paper we suggest the use of *U* of HbA1c as part of the quality control program of the clinical laboratory: (a) to validate that its HbA1c results are fit for clinical purposes only when *U* is below the suggested ± 0.5% uncertainty [8–10] and (b) to help clinicians in the interpretation of the results, as will be discussed in the next paragraphs. Additionally, the estimation of *U* on HbA1c measurement will help with the compliance of ISO 15189 requirements as can easily be calculated using the approach suggested in this work.

One of the reasons of why this parameter is not used in our field is the complexity of the method as originally indicated by GUM [14]. The first objective of the present study was demonstrate that the use of the EURACHEM/CITAC guide [7] in the calculation of uncertainty of HbA1c measurement can be used periodically in the clinical laboratory as it does not require complex statistical knowledge, only requiring data obtained from the laboratory's internal and external quality control, and its calculations are easy to perform. Additionally, as has been previously described [6], when calculating the uncertainty of a measurand such as HbA1c, the method bias and its related uncertainty must be taken into consideration. One of the major advantages of the approach used in this work to calculate the uncertainty of HbA1c measurement is that this method allows to incorporate in its formula the calculation of imprecision, bias, uncertainty of bias and uncertainty of the calibration; and as was shown in the current study, all these parameters contribute to the actual dispersion of the values that could be attributed to the measurand (See Table 4).

When a health care provider receives an HbA1c result of a patient, it is assumed that the result is within a certain range close to the true value of the measurand; however, Lenters-Westra et al. showed that even if a method is accredited by NGSP, not all HbA1c results are fit for their clinical purpose [14]. Additionally, “in some locations there is still a serious problem in HbA1c measurements as a result of a lack of

standardization of the methods in clinical routine laboratories" [15]. The knowledge of the uncertainty of an HbA1c measurement result would give the clinician the necessary confidence to determine with certainty the level of glycemic control of the patient, as this parameter helps in the interpretation of measurement results, especially when comparing a result with a decision limit [6]. As different national diabetes associations have recommended that the primary goal of diabetic therapy is an HbA1c level of < 7.0% (53 mmol/mol), while results of > 8.0% (64 mmol/mol) indicate a poor control, it has been estimated that to properly classify an individual with an HbA1c value of 7.5% (58 mmol/mol), the measurement error, or uncertainty of measurement, should not exceed ± 0.5% [8–10]. If *U* is greater, say 1.0%, a patient with an HbA1c result of 7.0% (53 mmol/mol) would mean that the true value of the measurement could range between 6.0% (42 mmol/mol) (Patient under good glycemic control) and 8.0% (64 mmol/mol) (Patient under poor control), situation that would classify the patient in both glycemic control categories, which is clinically unacceptable. Based on this example, it could be stated that a *U* higher than ± 0.5%, in the case of HbA1c, would not properly indicate if a patient is achieving the treatment goals established, what brings about a possible failure in the glycemic control of the individual and, therefore, a possible increase in the risk of developing diabetes complications.

In our case, there is a significant difference between the results of the uncertainty of measurement calculated using Unity (± 0.19%) and RIQAS (± 0.43%). Since the component of imprecision is the same for both approaches, the difference lies in the bias component of the formula, which was higher when the latter method was used. Ideally, to obtain a more realistic result of bias and, thus, a more accurate measurement of uncertainty, bias should be calculated using an accuracy-based proficiency testing program. However, in those laboratories where no such programs are available, based on the analysis of these results, we suggest to calculate *U* from the data generated by an interlaboratory program, such as Unity, rather than from a proficiency testing program, such as RIQAS, for two main reasons: (a) When calculating *U* from the results of a proficiency testing program, only one result a month is incorporated in the general equation, whereas when using an interlaboratory program such as Unity, the uncertainty estimate is obtained from a larger set of data (daily controls that in this study expand for 6 months); and (b) in the latter approach, as the data is generated every day, the uncertainty of measurement include the uncertainty of the test results across as many routine operating conditions as possible (multiple reagent batches, multiple operators, variations in the conditions of the environment and instrument maintenance), thus including more variables that generate a result that reflects a closer value of the true uncertainty of measurement.

As suggested by Farrance et al. [6] and confirmed in different measurands by Padoan et al., in a paper that does not described in fully the measurands analyzed [16], when *U* is calculated in a measurand whose test results will be compared to clinical decision limits, bias plays a significant role in the total component of uncertainty. In our work, we confirm this finding specifically for the case of the uncertainty of HbA1c measurement, as the bias component of uncertainty is as large of a contributor as that of imprecision, including that of the uncertainty associated to the calibrators and that of the reference value, RMS ($u_{(Cref)}$), that albeit small, is a contributor of the total uncertainty of the test result (See Table 4).

One of the major limitations of the current study is that when assessing measurement bias, ideally, it should be estimated using reference materials; unfortunately, neither the Unity nor the RIQAS programs are accuracy-based programs and the "reference values" are established using the robust average of the results reported by all participants. However, using reference materials is not frequently practicable and realistic for medical laboratories, especially for small to mid-size ones from developing countries, thus determination of bias based on consensus value represents a valid alternative and it may well be the only information readily available [16,17]. As this "reference value" incorporates additional uncertainty to the HbA1c measurement, its own uncertainty ($RMSu_{(Cref)}$) must be calculated according to 2.2.3 and, in order to obtain a more robust value of *U*, be incorporated into the total bias component of the formula (See Table 4). A second limitation of our study is that the commutability of control samples was not tested and therefore a matrix related bias could not be excluded.

The clinical importance of the determination of uncertainty of measurement of HbA1c, and the reason why we suggest to include such result in the final report of the patient, is that based on the result of *U*, the clinician can determine the validity of the test result by establishing with certainty the range where the true value of the patient's HbA1c concentration lies. For example, based on our *U* results obtained with the interlaboratory program approach, the true value of the glycated hemoglobin concentrations of two individuals with reported HbA1c of 7.0% (53 mmol/mol) and 8.0% (64 mmol/mol), would oscillate in the range of 6.81% (51 mmol/mol) – 7.19% (55 mmol/mol) and 7.81% (62 mmol/mol) – 8.19% (66 mmol/mol), respectively, indicating, without ambiguity, whether the patient has achieved the proper glycemic control goals. Different studies have been published on the calculation of *U* on different clinical chemistry analytes [6,14,16]; however, literature on uncertainty of measurement on analytes such as HbA1c, whose results are compared to established clinical decision points rather than to reference values, using the EURACHEM/CITAC approach is scarce [18].

5. Conclusions

In conclusion, based on the recommendation of ISO 17025 [13], further adapted to the clinical laboratory by the Australasian Association of Clinical Biochemists [19], to apply the concept of uncertainty of measurement to medical testing only when of practical relevance to both the laboratory and the clinical users of the test results, the periodical calculation by the clinical laboratory of the uncertainty of measurement of glycated hemoglobin meets both criteria, and thus, is strongly recommended to be included in the quality control program of the laboratory. Firstly, with its periodical calculation, and comparing the obtained results to the suggested maximum value of ± 0.5%, the clinical laboratory would have an additional tool to assure that its HbA1c results achieve the proper analytical performance specifications and guarantee that they are fit to properly evaluate the glycemic control of an individual. Secondly, with the inclusion of the uncertainty of measurement result on the final report of the patient, a clinician could easily determine the level of confidence that can be placed in the test results, understand its limitations and reliably make the necessary adjustments in the treatment of the diabetic patient.

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Declarations of interest

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Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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