INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2024.81894
Int J Med Biochem 2024;7(2):45–50

Research Article

25-hydroxyvitamin-D3 analysis with high-performance liquid chromatography in terms of total analytical error and measurement uncertainty

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Abstract

Objectives: Ensuring the accuracy and consistency of data obtained in the biochemistry laboratory is essential for obtaining reliable and comparable results. This study aims to calculate total analytical error (TAE) and measurement uncertainty (MU) values to assess the analytical performance of the 25-hydroxyvitamin D3 (25-OH vitD3) analyte measured using high-performance liquid chromatography (HPLC) in our laboratory.

Methods: In our study, the internal quality control (IQC) results, which were analyzed at two levels daily between 01–01.2022–31.12.2022, and the data of the external quality control (EQC) program, which was performed at two levels per period for four periods per year, were retrospectively examined for the MU and TAE calculations of the 25-OH vitD3 analyte. TAE was calculated by the formula TAE% = Bias% + (1.65×CV%). MU has been calculated adhering to the Nordtest guideline.

Results: In our study, while TAE values and U value calculated using EQC data for bias and u(bias) calculation were found to be higher than the analytical performance goals we used in our study, TAE values and U value calculated using IQC data for bias and RMSbias calculation were found to be lower than the analytical performance goals we used in our study.

Conclusion: Clinical laboratories should evaluate analytical performance at regular intervals using appropriate methods. In cases where the number of participants using the same method and device in the EQC program is low, we recommend that EQC data not be used in the calculation of the bias component when evaluating analytical performance with TAE or MU.

Keywords: Allowable total error, analytical quality management, clinical chemistry, measurement uncertainty, total analytical error

How to cite this article: Seyithanoglu M. 25-hydroxyvitamin-D3 analysis with high-performance liquid chromatography in terms of total analytical error and measurement uncertainty. Int J Med Biochem 2024;7(2):45–50.

Clinical laboratories play a crucial role in diagnosing, treating, and monitoring diseases. Ensuring the accuracy and consistency of data obtained in the biochemistry laboratory is essential for obtaining reliable and comparable results.

Scientifically, all measurement results, including those from clinical laboratories, inherently contain some degree of error. To evaluate analytical performance characteristics, clinical laboratories utilize parameters such as total analytical error (TAE), bias, coefficient of variation (CV), and uncertainty of measurement (MU) [1].

The concept of total analytical error was introduced by Westgard et al. [2] in 1974, defining error in clinical laboratory results. TAE combines imprecision and bias in a test result, encompassing both random and systematic errors [3]. Tradi-

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Submitted: December 11, 2023 **Revised:** January 23, 2024 **Accepted:** January 26, 2024 **Available Online:** April 22, 2024

tionally, bias and imprecision (CV) are linearly added in TAE detection, represented as TAE=bias+z.CV, where the value establishes the range around the "true" value of the measured analytical results with a specified probability, often 95% [4].

The Guide to the Expression of Uncertainty in Measurement (GUM), published in 1995, introduced the measurement uncertainty concept [5]. ISO standards, such as ISO 15189, mandate laboratories to determine uncertainty for each test [6]. Measurement uncertainty can be assessed through bottom-up or top-down approaches. The bottom-up approach involves identifying all uncertainty components for subsequent calculation, while the top-down approach utilizes internal and external quality control data for practical uncertainty estimation [7]. The Nordtest approach provides a practical and understandable method for uncertainty estimation [8].

Quality, defined as conformity to requirements, is evaluated by comparing measured performance with intended use requirements [9]. Models like the Clinical Laboratories Improvement Amendments (CLIA) and data from organizations like the College of Pathologists of Australasia (RCPA) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) are instrumental in setting quality targets [10, 11].

It is known that vitamin D plays an important role in various physiological processes, especially bone metabolism, and its deficiency is associated with many diseases in humans [12]. Vitamin D is transported in the circulation mainly as vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) by binding to vitamin D binding-protein. 25-hydroxyvitamin-D3 (25-OH-D3), which accounts for more than 95% of measurable vitamin D in serum with its relatively low biological variation and long half-life, is considered the analyte of choice in the assessment of vitamin D status [13]. Nowadays, 25-OH-D3 measurement depends on different measurement techniques such as high-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectrometry (LC-MS/MS), or immunosorbent (ELISA), chemiluminescence (CLIA), electrochemiluminescence (ECLIA). While chromatographic methods are acknowledged as the gold standard for measuring low concentrations of analytes in serum, the time-consuming sample pretreatment procedures associated with chromatography to measure 25(OH)D metabolites have led to the widespread use of electrochemiluminescence methods. Despite drawbacks like cross-reactivity between the D2 and D3 forms of antibodies, these electrochemiluminescence methods are favored due to their efficient and rapid workflow [14].

This study aims to calculate TAE and MU values to assess the analytical performance of the 25-hydroxyvitamin D3 (25-OH vitD3) analyte measured using high-performance liquid chromatography (HPLC) in our laboratory. The results will be compared to the desirable biological variation database specification for total allowable error (TEa) from EFLM [15] and the desirable analytical performance specification for standard measurement uncertainty according to Braga et al.'s [16] article.

Materials and Methods

25-OH vitD3 analyses were carried out on an HPLC device (Thermo Ultimate 3000, ABD) using the Vitamin D ClinRep HPLC kit (Recipe Chemicals & Instruments, Munich, Germany) at the biochemistry laboratory of Training and Research Hospital. In our study, the internal quality control (IQC) results, which were analyzed at two levels daily between 01–01–2022 and 31–12–2022, and the data of the external quality control (EQC) program (Instand, Düsseldorf, Germany), which was performed at two levels per period for four periods per year, were retrospectively examined for the MU and TAE calculations of the 25-OH vitD3 analyte. Instand External Quality Assessment Scheme distributes human serum samples four times per year to between 272–337 participants worldwide for the determination of total serum 25-OH-D3 with 8 participants in peer group. Each level of IQC material had the same lot number throughout the study. EQC results were within acceptable limits in all periods, and no exclusions were made. No human or animal biological material was used in the study.

Analytical performance characteristics

Calculation of total analytical error (TAE): Total analytical error was calculated separately for both levels of IQC material using the following formula:

TAE%=Bias% + (1.65×CV%)

The CV% of IQC samples analyzed at two levels on each analysis day was calculated separately for both levels of IQC material using the following formula (a). In our study, three separate bias calculations were made using IQC and EQC data. In addition to the bias calculation using the peer group EQC data using the formula (b) below, a separate bias calculation was made using the formula (c) below with the EQC data of all participants due to the low number of peer group participants. The absolute values of the calculated biases were summed and divided by the total number of EQC analyses, and the bias value used in the total analytical error formula was obtained. In addition, the bias was calculated separately for both levels of IQC materials using the following formula (d) with the results obtained from the IQC samples. The mean value declared by the manufacturer was used as the target value in the bias calculation from the IQC material.

a. CV% = (Standard Deviation/mean)×100
b. Bias% = [(laboratory result – mean of peer group)/mean of peer group]×100
c. Bias% = [(laboratory result – mean of all participants)/mean of all participants]×100
d. Bias% = [(mean of IQC results – target value)/target value] ×100

Calculation of measurement uncertainty: The Nordtest guide, which is a more useful and practical method for clinical laboratories in calculating uncertainty, recommends using both internal and external quality control results. In our study, the calculation model defined in the Nordtest guide was used to calculate measurement uncertainty[8]. Calculations were made step by step.

Step 1: Calculation of the intra-laboratory repeatability (Rw) component of uncertainty: To express the uncertainty coming from the analytical process, arithmetic mean, SD, and CV% values were calculated separately for each level (L1, L2) using daily internal quality control data. The obtained CV% values were substituted into the formula below, and the repeatability uncertainty component (Rw) was calculated. The standard uncertainty u(Rw) value was obtained by dividing the Rw value by two.

$Rw = \sqrt{[(CVL1)^2 + (CVL2)^2]} / n$

$u(Rw) = Rw/2$

Since each level of IQC materials had the same lot number throughout the study, a total of two CV% values were obtained, one for each level (n=2).

Step 2: Calculation of the bias component of the uncertainty u(bias): It indicates the standard uncertainty of the bias value and is divided into two: laboratory (RMSbias) and material (u(Cref)) bias.

$u(Bias) = \sqrt{(RMSbias)^2 + u(Cref)^2}$

Calculation of RMSbias (Laboratory bias): Three different RMSbias calculations were made with three different bias values calculated using the IQC data and the EQC data of all participants and the peer group. When using IQC data, the average of the absolute values of the biases calculated for both levels of IQC materials was used as the RMSbias value. The following formula was used to calculate RMSbias with the results obtained from EQC samples.

$RMSBias = \sqrt{\Sigma(bias)^2} / n$

The "n" value in the formula refers to the number of biases in the year obtained from the EQC evaluation results.

Calculation of u(Cref) (Material-induced bias): u(Cref) is defined as the uncertainty component obtained from certified reference material or by calculating the actual or expected value from external quality control results. Three different u(Cref) values were obtained using the uncertainty data obtained from the calibration and the EQC data of all participants and the peer group.

The following formula was used to calculate the u(Cref) value from EQC data. When the u(Cref) value obtained with this formula was used, u(Bias) calculations were made with the RMSbias value calculated from EQC data.

$u(Cref) = CV_{mean}/\sqrt{nLab}$

In the EQC report, bias and CV% values are reported as calculated to contribute to measurement uncertainty calculations. CV% values obtained from EQC reports were used. For each period and level, the CV% values of peer or all group in the EQC report were summed and divided by the number of CV% obtained. CV_{mean} was obtained. The number of participants of peer or all group was summed and divided by the number of periods in the EQC program. nLab value was obtained.

In addition to the u(Cref) value calculated from EQC data, the uncertainty data from calibration was also used for the u(Cref) value. In this case, the RMSbias value calculated from IQC data was used in u(Bias) calculations. A single level calibrator is used in the analysis of 25-OH vitD3. For the uncertainty value from the calibration, the information in the calibrator package insert was used: The uncertainty of the mean value is ±2.3% at a 95% confidence level.

Step 3: Calculation of the combined standard uncertainty (uc): Using u(Rw) and u(bias), the combined standard uncertainty (uc) was calculated using the formula below.

$uc = \sqrt{[u(bias)^2 + u(Rw)^2]}$

Step 4: Calculation of the expanded uncertainty value (U): The expanded uncertainty value was calculated by multiplying the combined standard uncertainty value by the k factor. The value 1.96 was taken for k, which represents the 95% confidence interval.

$U = k \times uc$

All calculations were made using Microsoft Office Excel (Microsoft Corporation, Redmond, WA, USA).

Analytical Performance Goals

Total allowable error (TEa): As the TEa value, the desirable biological variation database EFLM specification for TEa was used [15]. Permissible limits of measurement uncertainty

In our article, the desirable analytical performance specifications for standard measurement uncertainty in the article by Braga et al. [16] were used. The expanded uncertainty limit was determined by multiplying this standard uncertainty value with the value of 1.96, which represents the 95% confidence interval.

Results

The determined total analytical error (TAE) values, obtained by utilizing EQC data from a peer group for bias calculation, were identified as 23.89 and 20.36 for L1 and L2, respectively. Similarly, when TAE values were calculated using EQC data from all participants for bias calculation, the results were 27.71 and 24.18 for L1 and L2, respectively. In contrast, TAE values derived from IQC data for bias calculation were 12.30 and 8.73 for L1 and L2, respectively. Our study employed a TAE analytical performance goal of 12.40, as outlined in Table 1-3.

The determined uncertainty (U) value, calculated by using EQC data from a peer group for the calculation of u(bias), was identified as 32.58. Similarly, when the U value was calculated using EQC data from all participants for the computation of u(bias), the result was 35.77. Furthermore, the U value, calculated using IQC data for RMSbias calculation and incorporating the uncertainty value from calibration for u(Cref), was established at 6.31. In our study, the analytical performance goal for U was set at 19.60, as indicated in Table 1-3.

Discussion

The assessment of analytical performance holds significant importance in the realm of quality management for clinical labora-

Table 1. Analytical performance characteristics and analytical performance goals (bias and u(bias) values were calculated using EQC data of peer group)

CV% (IQC L1)	CV% (IQC L2)	Mean of Bias% (EQC)	TAE (IQC L1)	TAE (IQC L2)	U	Desirable specification for TEa*	Permissible limits of U
7.42	5.28	11.65	23.89	20.36	32.58	12.40	19.60

*: Desirable biological variation database specification for TEa. EQC: External quality control; CV(%): Coefficient of variations; IQC: Internal quality control; L1: level 1; L2: level 2; TAE: total analytical error; U: expanded uncertainty; TEa: Allowable total error.

Table 2. Analytical performance characteristics and analytical performance goals (bias and u(bias) values were calculated using EQC data of all participitants)

CV% (IQC L1)	CV% (IQC L2)	Mean of Bias% (EQC)	TAE (IQC L1)	TAE (IQC L2)	U	Desirable specification for TEa*	Permissible limits of U
7.42	5.28	15.47	27.71	24.18	35.77	12.40	19.60

*: Desirable biological variation database specification for TEa.

Table 3. Analytical performance characteristics and analytical performance goals (Bias and RMSbias values were calculated using IQC data and u(Cref) value was calculated using the uncertainty value from calibration)

CV% (IQC L1)	CV% (IQC L2)	Bias% (IQC L1)	Bias% (IQC L2)	TAE (IQC L1)	TAE (IQC L2)	U	Desirable specification for TEa*	Permissible limits of U
7.42	5.28	0.06	0.02	12.30	8.73	6.31	12.40	19.6

*: Desirable biological variation database specification for TEa.

tories. Total Analytical Error (TAE) has been widely employed in clinical laboratories globally due to its practicality and straightforward mathematical model. Its simplicity and ease of calculation have notably influenced clinical chemistry, particularly in the United States, where the US Food and Drug Administration cites guidance from the Clinical and Laboratory Standards Institute based on the TAE approach for clinical laboratory testing [17]. While total error methods have firmly established themselves in laboratory medicine, other fields of metrology have shifted towards measurement uncertainty methods. It's worth noting that unlike measurement uncertainty, the concept of Total Analytical Error is not part of the International Vocabulary of Metrology (VIM) [18] or the Guide to the Expression of Uncertainty in Measurement (GUM) [5]. ISO 15189 specifically mandates the use of Measurement Uncertainty (MU) in calculations, although the standard doesn't provide explicit guidance on practical determination [6]. In response, ISO/TS 20914 has been published as a practical guide for estimating MU in clinical laboratories [19]. This technical standard takes a more practical "top-down" approach, in contrast to GUM's intricate mathematical models rooted in a "bottom-up" methodology.

There is controversy about the pros and cons of TAE and MU. The similarity between both models is that they both express the reliability of the test result from a different perspective. Regardless of the controversy on the pros and cons of TAE and MU, in our study we evaluated the analytical performance characteristics of the 25-OH vitD3 analyte in terms of TAE and MU. When calculating TAE in our study, we used different data sources for the bias component: IQC and EQC data. TAE results calculated with the bias obtained from EQC data were higher than TAE results calculated with the bias obtained from IQC data. In addition, while the TAE results calculated with the bias obtained from EQC data were higher than our analytical performance targets, the TAE results calculated with the bias obtained from IQC data were lower than our analytical performance targets. While our EQC results were within acceptable limits in all periods, we examined the root reason why the TAE results calculated with the bias obtained from EQC data were higher than the analytical performance targets: It was seen that the number of participants using the same method and device as us in the EQC evaluation program of which we are a member was 8. We think that the small number of participants is not suitable for both external quality assessment and analytical performance evaluation with TAE. Furthermore, given the absence of standardization in vitamin D measurement, we believe it would be inappropriate to compare our vitamin D results with those obtained through different methods in external quality assessment. Because of this, calculating TAE using the bias result derived from EQC data from all participants will not give accurate outcomes. Similar to the TAE calculation, we used different data sources for the RMSbias component in our MU calculation. Findings similar to our TAE results were

also present in the MU results. In the study conducted by Demir et al. [20] using the chemiluminescence immunometry method, they found the expanded measurement uncertainty for 25-OH vitD3 measurement to be 24%. Cavalier et al. [21], in their study using low, medium, and high serum pools on the Roche Elecsys device for measurement uncertainty of 25-OH vitD3, found the relative uncertainty values to be 22.4%, 20.9%, 14.8%, respectively. Basat et al. [22], in their study where they evaluated the measurement uncertainty of 25-OH vitD3 analyte with Liquid Chromatography-Tandem Mass Spectrometry, found the expanded measurement uncertainty to be 34.64%. In this study, the RMSbias component was calculated with EQC data. In our study, when the RMSbias component was calculated with EQC data, the expanded measurement uncertainty was found to be 32.58%. However, while the number of EQC program participants in our study was 8, the number of EQC program participants in Basat et al.'s [22] study was between 152–157.

To determine whether the measured performance aligns with quality standards, it must be compared to an analytical performance specification (APS) or target. EFLM has recommended a straightforward approach for determining the APS of an analyte. According to this approach, there are three models: model 1—clinical outcomes, model 2—biological variation, and model 3—state-of-the-art performance [23]. In general, it is favored to apply Model 2, where APS is based on BV [24]. As the TEa value, the desirable biological variation database EFLM specification for TEa was used in our study [15]. Quite recently, Cavalier et al. [25] conducted an investigation into Model 2, generally regarded as the most comprehensive approach, and Model 1 over the course of one week and three months. The objective was to evaluate the APS for MU necessary for detecting a significant or highly significant change in 25(OH)D3 concentration. Cavalier et al. [25] asserted that the conventional method of generating and applying Biological Variation (BV) data is inappropriate for 25(OH)D, given the seasonal fluctuations in analyte levels. They suggested an alternative approach. Considering the physiological changes in 25(OH)D3 concentrations over time, they proposed the APS for MU as follows: 9.6% to detect a difference at $p<0.01$ (defined as 'desirable' MU). Braga et al. [16], in their article where they presented the performance characteristics of measurement uncertainty of common biochemical measurements according to Milan models, stated that the desirable specification for MU according to model 1 in vitamin D measurement was 10%. In our article, the desirable analytical performance specifications for standard measurement uncertainty in the article by Braga et al. [16] were used.

Variations in vitamin D measurement methods and the absence of standardization in calibrators pose challenges in establishing a single cut-off point, leading to discrepancies among laboratories. Given that the diagnosis of 25(OH)D3 deficiency relies heavily on the measurement outcome in conjunction with the clinical condition, achieving comparable results across laboratories is currently unattainable due to substantial disparities in measurement methods and the absence of measurement uncertainty incorporated into the results [26]. Consequently, when reporting the 25(OH)D3 measurement outcome, it is essential to also provide the measured or calculated measurement uncertainty [27]. The inclusion or exclusion of the measurement uncertainty value can result in new values, potentially altering the diagnostic categorization of patients from severe deficiency to a sufficient level [22].

Conclusion

As a conclusion, clinical laboratories should evaluate analytical performance at regular intervals using appropriate methods and produce solutions to error sources in line with the findings they obtain. In line with our results in this study, we would like to emphasize that laboratories should pay attention to the number of participants using the same method and device during the membership phase of the external quality control program. In cases where the number of participants using the same method and device in the EQC program is low, we recommend using IQC data to calculate the bias component when evaluating analytical performance with TAE or MU.

Conflict of Interest: The authors declare that there is no conflict of interest.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

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