Received: 16 November 2021 | Revised: 2 May 2022 | Accepted: 9 May 2022

DOI: 10.1002/jcla.24521

RESEARCH ARTICLE

WILEY

Measurement comparability of insulin assays using conventional immunoassay kits

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Funding information
Korea Research Institute of Standards and Science, Grant/Award Number: KRISS 22011067

Abstract

Background: The standardization of measurement aims to achieve comparability of results regardless of the analytical methods and the laboratory where analyses are carried out. In this paper, a comparison of results from several immunoassay-based insulin analysis kits is described, and the steps necessary to improve comparability are discussed.

Methods: Four manual enzyme-linked immunosorbent assay (ELISA) kits produced by Mercodia, Alpco, Epitope Diagnostics, and Abcam, and three automated chemiluminescent (CLIA) insulin assay kits (Siemens Centaur XP, Unicel Dxl800, Cobas e801) were compared by analyzing human serum samples and certified reference materials for human insulin.

Results: The seven evaluated assay kits showed substantial discrepancies in the results, with relative standard deviation ranges between 1.7% and 23.2%. We find that the traceability chains and the unit conversion factors are not yet harmonized, and current reference materials for insulin are not applicable for immunoassay-based method validation due to the use of different matrices.

Conclusions: The findings suggest the need to fine tune insulin analysis methods, measurement traceability, and any conversion factor used in post-analysis steps in accordance with the necessity for standardization.

KEYWORDS
CLIA, comparability, ELISA, immunoassay, insulin, standardization, traceability

1 | INTRODUCTION

Immunoassays are analytical methods that achieve the detection and quantification of analytes, particularly peptides and proteins in biological samples, through the formation of a stable complex between the analyte and a specific antibody. They represent very selective and sensitive techniques that have found application in several areas such as clinical chemistry, bioanalysis, pharmaceutical analysis, toxicological analysis, and environmental analysis.[1–3] Owing to their capacity for high throughput and significantly reduced average analytical times, through the simultaneous analysis of numerous samples with ultimate detection sensitivity, immunoassays are the preferred platform for most protein studies, particularly clinical diagnostics and drug development where specificity is critical.[4–6] Among various immunoassays, the most commonly employed in routine clinical settings are the enzyme-linked immunosorbent assay (ELISA)

and chemiluminescence immunoassay (CLIA) methods for their cost-effectiveness and high throughput.[4–7] In fact, the overall immunoassay technique has been subdivided into numerous specific methods, so that rapid commercialization has occurred through *kits* unique to each manufacturer. Currently, there is a wide range of commercial kits available for immunoassay-based protein analysis.

One of the most commonly analyzed proteins is insulin, a representative peptide hormone that regulates the absorption of glucose in the body and is also the main anabolic hormone. Defects in the production of insulin lead to several different types of diseases, with the most common condition being diabetes mellitus categorized by chronic hyperglycemia. The concentration of insulin may improve the classification and management of diabetes mellitus and assess β-cell secretion and insulin resistance. Therefore, reliable quantification of insulin is critical for clinical purposes such as the diagnosis and treatment of related diseases, as well as for research and manufacture; accordingly, more accurate and sensitive detection of insulin is required.[4,8–11] Analytical methods for insulin can be generally divided into three categories by analytical principle, namely immunoassays, chromatography, and electrochemical biosensors. While each method has pros and cons in insulin analysis according to its applications, the immunoassay-based methods are the most commonly adopted in routine clinical testing for their strength in high throughput, detection sensitivity, and selectivity with reliable cost, although improvement is still needed in terms of the results comparability between analytical procedures, and specificity of recombinant insulin analogues.[4,8–10,12]

The purpose of this work was to investigate several different kits in terms of measurement comparability in insulin immunoassay-based quantification. Not only for bioanalytical applications but also in clinical settings, regardless of when, where, and how the testing is conducted, it is critical to have comparable insulin results between different assays, as discrepancies have been shown to lead to retesting, unverified results, and even misdiagnosis with unnecessary resource abuse.[4,5] Insulin has quite a long history of standardization trials, with successful achievements in several big pilot studies organized by the American Diabetes Association and the International Federation of Clinical Chemistry.[8,11–13] The implementation of measurement traceability through a reference system provides one of the most important tools that supports the standardization process in laboratory medicine.[14] We focused on currently available and widely adopted kits in both research and hospital settings, and found several points of discussion related to result comparability in insulin analysis. The packaged calibrators were compared with LC–MS. Available certified reference materials (CRMs) for human insulin were also investigated in order to validate the kits. The points discussed in this study are major factors to improve results comparability in protein analysis not only for between immunoassays, but also for between measurement procedures of different principles, and the results underpin our knowledge about establishment of results comparability.

2 | MATERIALS AND METHODS

2.1 | Chemicals

Four ELISA kits for human insulin (10-1113-01, Mercodia; 80-INSHU-E01.1, Alpco; KT-886, Epitope Diagnostics; ab200011, Abcam) were purchased from the respective manufacturers. Three CLIA kits were equipped with fully automated analyzers (Siemens Centaur XP, Siemens Healthineers; Unicel Dxl800, Beckman Coulter Diagnostics; Cobas e801, Roche Diagnostics) including reagents and necessary parts.[15–17] All kits are intended to be used to research and in-vitro diagnosis depending on regional permission. Pooled human serum was obtained from Innovative Research (Canada) followed by homogenization, filtration, and aliquots in-house protocol (Supporting Information). Human insulin certified reference materials (CRMs) were purchased from the National Metrology Institute of Japan (NMIJ CRM 6209-a) and Cerilliant Corporation (I-034).[18] Both serum and CRMs were stored at −70°C prior to use. Bovine serum albumin (BSA), HPLC-grade acetonitrile, formic acid, and trifluoroacetic acid were obtained from Sigma-Aldrich. The water used in this study was produced using a Millipore Alpha-Q water purification system (Millipore) with a filtration through a membrane filter (pore size 0.2 μm, Nylon) under vacuum.

2.2 | Instruments

A multimode plate reader (EnSpire® system, PerkinElmer) was used for the manual ELISA assays.

The LC–MS system for insulin analysis was a 5600+ TripleTOF with a dual-spray source (ABSciex) and nitrogen generator (Genius XE SMZ, PEAK Scientific), coupled with a Nanospace SI-2 series UHPLC composed of a dual pump, column oven, and autosampler (Shiseido). Separation of human insulin was carried out using an Accucore C18 column (2.6 μm, 50 × 2.1 mm i.d., Thermo Fisher Scientific) with 0.1% v/v FA in water, and ACN as mobile phases A and B, respectively. The human insulin was detected at *m/z* 1162.5 $[M+H]^{5+}$. The detailed analytical conditions are also shown in Table S1.

2.3 | Sample analysis for immunoassay

All materials and prepared reagents were equilibrated at room temperature prior to use in accordance with each manufacturer's instructions for each kit. For CLIA analysis, the entire procedure was fully automated without any pretreatment before loading onto the instruments. In the manual preparation for the ELISA assays, generally, samples and standards were firstly added to plate wells. Next, antibody cocktails were added into the wells containing the samples and standards. The detailed preparation conditions were in accordance with the protocols of each manufacturer. The final samples were analyzed with a UV plate reader.

2.4 | Standard and sample preparation

Serum sample used in this study is pooled serum from multi donor followed by homogenization in the Supporting Information. Frozen serum were thawed and equilibrated at room temperature before analysis. At least three serum samples were analyzed on three consecutive days for intra- and inter-day assays to check the measurement precision of each kit.

The human insulin CRMs were also prepared with serial dilution using water down to the range 0–12 nmol/L, which is equivalent to 0–2000 μIU/ml based on the conversion factor of 1 μIU/ml = 6.00 pmol/L.[19] Additionally, the CRMs were also prepared with different diluents, such as 0.1% w/v BSA and human serum. The endogenous insulin in diluents were confirmed in each kit, and the results were subtracted as blank level. The concentrations of the samples were 0, 0.11, 1.08, 2.70, 5.40, and 10.8 nmol/L as prepared values of human insulin from the certified values. The samples were analyzed to check the matrix effects using four manual ELISA kits.

3 | RESULTS AND DISCUSSION

3.1 | Comparison with serum sample

The pooled serum samples were measured by seven kits; Figure 1 shows the measurement results. The results were spread from 18 pmol/L to 150 pmol/L, and the RSD in each kit showed ranges from 1.7% to 23.2%, which may relate to the procedure being manual or automated.[3] Although the kits were validated and ready to use with no necessity for further verification, the measurement precision was re-confirmed by comparing the results of serum samples in order to remove any doubt in operation. For this, three runs with three replicates each were processed over three consecutive days. Table 1 summarizes the intra- and inter-day assay results, with all of the results showing acceptable precision. This indicates that the discrepancies in the serum results were not caused by random error but rather by systematic bias among all the kits. Particularly for kit A, two different data set are shown in Figure 1 as two different lots showed different ranges of results. The results in Table 1 are only used one of the lot. Including the within kit variations, the measured values of insulin were spread across the border lines of the clinically recommended reference ranges[20–23], and the results indicate possibility that diagnostic decisions and scientific discussion can vary depending on the kit selection in insulin measurement. Interestingly, we found two different references traceable to two different WHO International Standards (IS), IS 83/500 and IS 66/304. Assays C and D were traceable to IS 83/500, which presents strong evidence for their lower results than those of other kits. The form of the IS 83/500 standard is human insulin crystals prepared from the enzymatic modification of porcine insulin, while the IS 66/304 standard comes from purified human pancreatic insulin. Unfortunately, we were unable to figure out the reason for the relatively lower level of the IS 83/500 traceable kits, and it should be noted that both batches of IS 83/500 and 66/304 have been exhausted and replaced by IS 11/212. Fortunately, the IS 11/212 standard, which is the only commercially available WHO IS, serves information about comparability with IS 66/304, the previous batch. However, kits C and D are still commercially available with traceability to different IS, and therefore users need to check the traceability served by the manufacturer, not only between kits from different manufacturers but also within kits of different lot numbers.

3.2 | Comparison of calibrators

LC–MS was used to check the quality and quantity of the insulin in the calibrators. First, the character of insulin was assessed as an intact form. Each ELISA kit or CLIA system for insulin assay is packaged with its own calibrator or serves very specific information about an accessible calibrator kit with no assessment in cross accessibility. Indeed, each calibrator from different kits showed a different character in color, concentration range, preparation protocol, etc. In several preliminary trials with the manual ELISA kits, the results were neither comparable nor acceptable by using different calibrators from different manufacturers (Table S1). It is supposed to have its own specific characters in immunoactivity as some kits serve additional information on cross activity with insulin analogues. In summary, no reasonable differences were detected between kits in LC–MS analysis. In MS spectrum, all the insulin in all calibrators showed exactly same pattern with m/z 1162.5 $[M+H]^{5+}$ (Figure S1). We adopted qToF MS to scan MS spectra in whole experiments obtaining better resolution. The results showed that the insulin samples are not different from human insulin characterized in CRM, although with different traceability in quantity assessment. Moreover, no related or interference protein-related compound were detected near insulin peaks in MS detection. The calibrators were additionally analyzed via LC–MS to confirm the absolute quantity by comparison with the human insulin CRM, but we could not obtain any reasonable results with several trials by two possible reasons. First, the highest concentration of the calibrators was claimed lower than 2 nmol/L, which was the detection limit of the LC–MS system used. And lastly, other protein measurement methods such as quantification via acid or enzyme reduction were not accessible as we do not have detailed information on the content of each calibrator.[24]

3.3 | Conversion factors in concentration of insulin

The conversion factors of the kits in this study are as follows. All the ELISA kits recommended a conversion factor of 6.0, while the CLIA kits recommended 6.945 (Kit E, Kit G) or 7.0 (Kit F). As IU is not traceable to the International System of Units (SI), several investigations into insulin standardization have recommended to use the SI unit pmol/L rather than IU/ml.[11,20] Figure 2 presents the results of applying a single conversion factor of 6.00 for the results in Figure 1 that reflect the multiple conversion factors recommended by the manufacturers (6.00, 6.954, and 7.00). At present, two

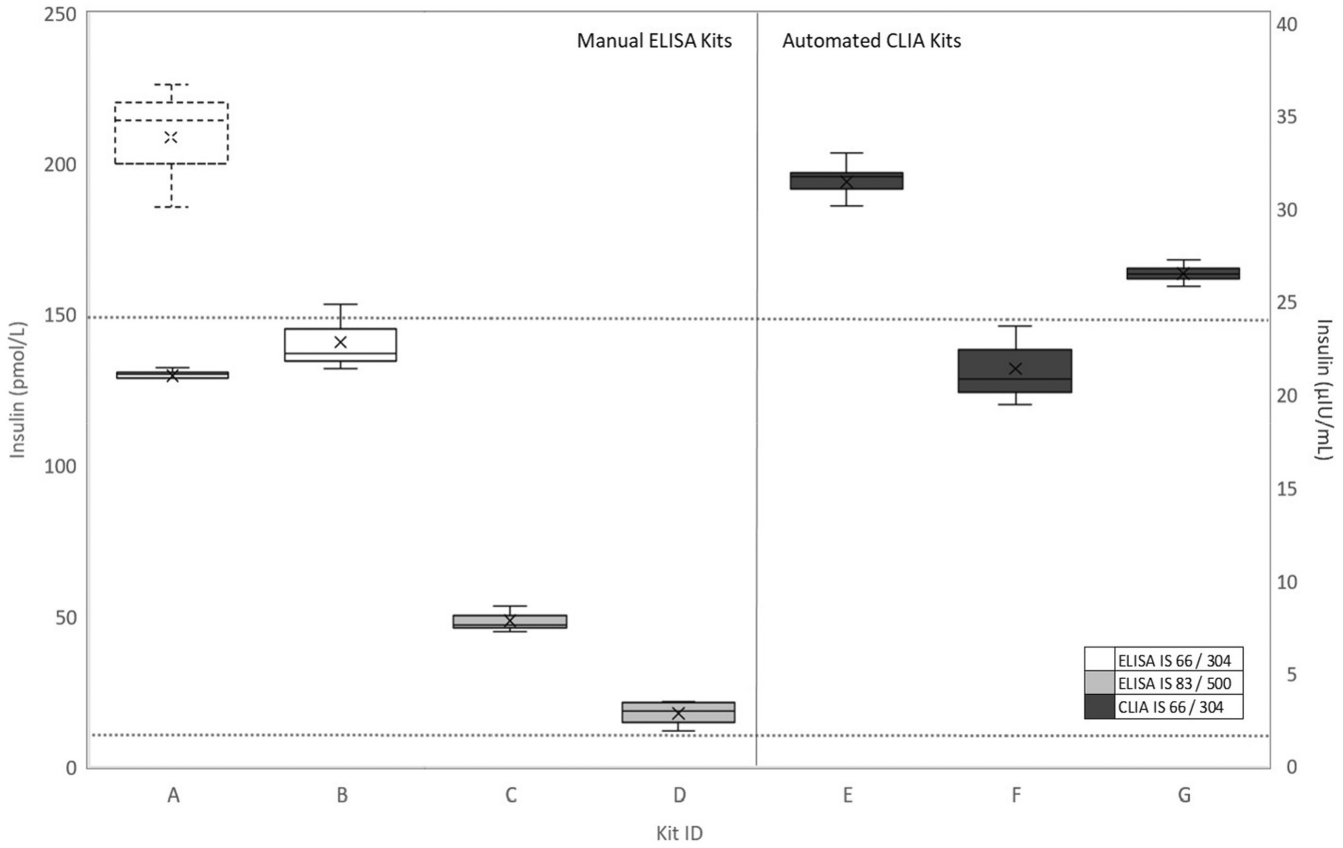


FIGURE 1 Human insulin analysis in serum by two different assay methods. Box plots represent distributions of measured values. A to D are the results from ELISA manual kits, while E to G are the results from CLIA automated analyzers. White boxes represent ELISA kits traceable to IS 66/304, and light gray boxes are ELISA kits traceable to IS 83/500. The dark gray boxes are CLIA assays traceable to IS 66/304. The 'X' represents the mean value, the line in the box represents the median value, and error bars represent the highest and lowest value. *Y*-axes represent pmol/L and μIU/ml, respectively. Multiple conversion factors were used in unit conversion; 6.0 for kits A to D, 6.945 for kits E and G, 7.0 for kit F. For kit A, two data set with different lot numbers were used

TABLE 1 Measurement precision of intra- and inter-run tests with the serum samples using different immunoassay kits

	Intra-run precision		Inter-run precision	
Kit ID	Measured value (mean ± SD[a], μIU/ml)	RSD (%)	Measured value (mean ± SD[b], μIU/ml)	RSD (%)
A	21.66 ± 0.03	0.1	21.60 ± 1.07	4.9
B	23.25 ± 0.45	1.9	23.92 ± 1.39	5.8
C	9.05 ± 1.78	19.7	8.90 ± 1.35	15.2
D	5.16 ± 0.15	3.0	4.88 ± 0.40	8.3
E	28.62 ± 0.57	2.0	28.38 ± 0.22	0.8
F	17.80 ± 0.23	1.3	18.65 ± 0.76	4.1
G	23.85 ± 0.49	2.1	23.68 ± 0.14	0.6

[a]Standard deviation of measured values in three repeated runs.

[b]Standard deviation of the average of the intra-run results over three consecutive days.

different units can be used in insulin assays, μIU/ml and pmol/L. The IU unit, namely hormone bioactivity, is commonly adopted in clinical and biological purposes, while the pmol/L unit has priority in metrological measurement systems as it is SI traceable.[8,13,25] The certified values of CRMs are served with SI by assessment of purity and quantification using LC–MS for amino acid analysis via acid hydrolysis, a primary method for protein quantification in terms of metrological hierarchy.[24] The new WHO IS for human insulin (IS 11/212) is also primarily served with an SI-based quantity (mg) with measurement uncertainty, rather than IU.

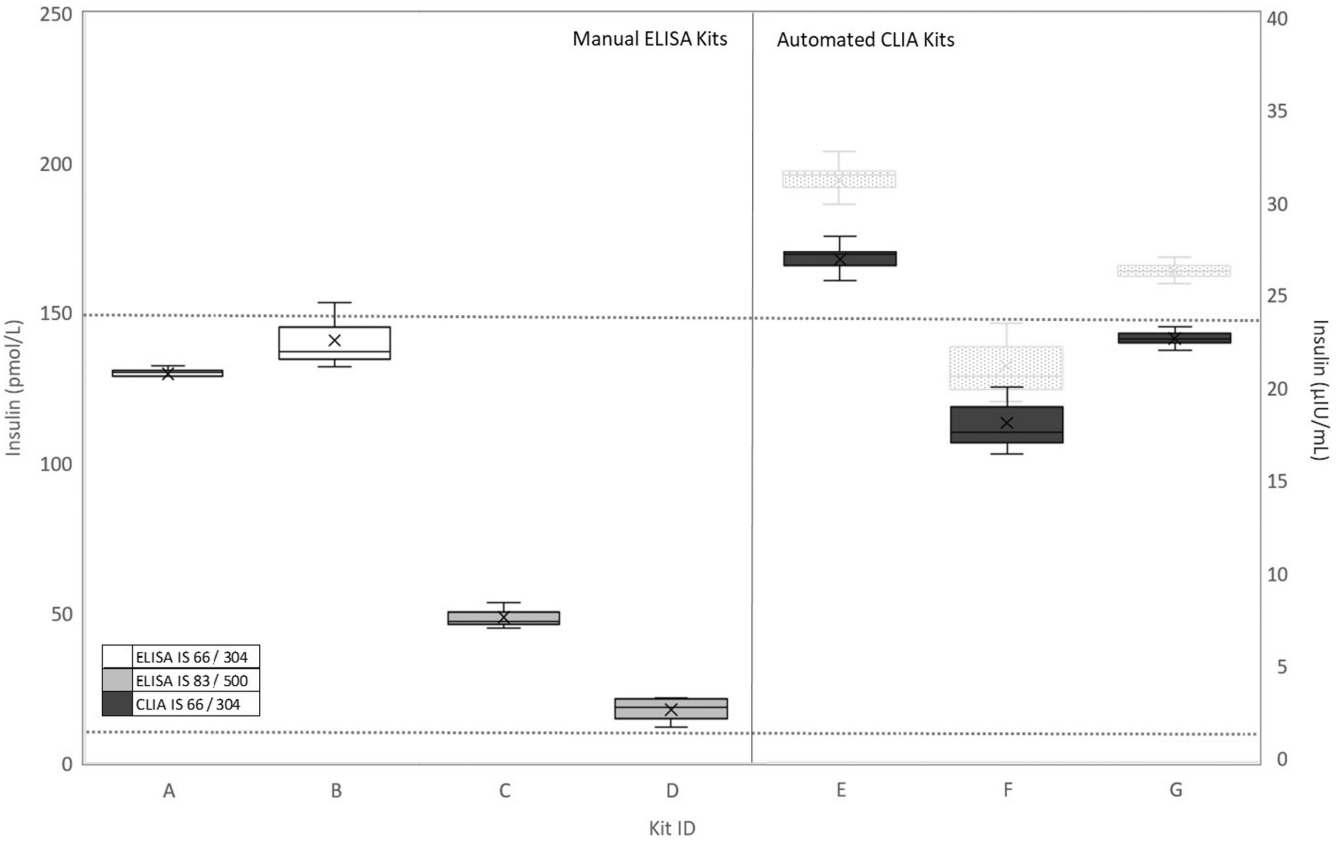
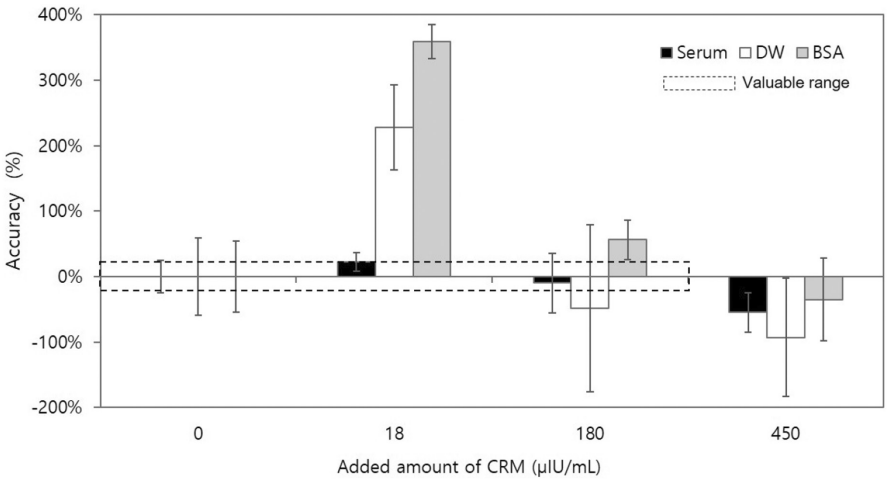


FIGURE 2 Human insulin serum analysis by two different assay methods with a single conversion factor between units. The results and descriptions are the same as Figure 1 except for applying a single conversion factor of 6.0 pmol/L to 1 μIU/ml. Dot boxes are shadows of the results in Figure 1, obtained with the various conversion factors recommended by the manufacturers

FIGURE 3 Accuracy assessment by recovery of found amount to gravimetrically fortified amount of CRM in four ELISA kits. Results were calculated by subtraction of blank value (0). Error bars represents standard deviation of average value between kits, not measurement precision within kit. Dotted line indicates an overall recommended dynamic range of kits (up to 200 μIU/ml) and acceptable accuracy cut-off range (within 20% difference)



Even a harmonized conversion factor are recommended, 6.00 pmol/L, there are still several different conversion factors available depending on the manufacturer or field.[19] While it is premature make definitive conclusions from this limited case, our results indicate that diagnostic decisions may vary with this type of simple change in data processing. Reaching a straightforward consensus in data processing can improve the comparability of measured values from various kits and systems.

3.4 | Matrix effect

We also performed an analysis of matrix effects using diluted CRMs with three different matrices; the results are shown in Figure 3. Both DW and BSA dilution results showed no trend or correlation with concentration change, while the measured values of the serum-based diluted CRM samples agreed with the expected values within the analytical range of the kits (2–200 μIU/ml). Considering the variability of the serum results

across the seven assays, we then used CRMs to investigate comparability based on certified values. As a primary reference material of lyophilized human insulin in buffer that is used to calibrate and validate measurement procedures, the employed CRMs are adept materials to compare the measurement results of different assays.[26] Although CRMs should ideally be commutable across different methods, for which the matrix is the major factor, presently there is no clear statement about commutability for immunoassay-based analysis in currently available CRMs of human insulin. Moreover, there is a significant gap in the concentration ranges between the typical clinical range and the studied CRMs, namely <150 pmol/L compared to >13.4 μmol/L, respectively, which means that repeated dilutions with increments of uncertainty and untraceable loss prevent any meaningful insight into comparability.

The following two major points can be discussed from the CRM trials. The first is the different definitions of measurement target in the certification method and immunoassays. Unfortunately, the points of view for protein in measurements by LC–MS and by immunoassays are not same, being based on amino acid sequence and activity, respectively. Additionally, only buffer solution-based human insulin CRM is currently available, a critical point in terms of commutability in clinical applications as mentioned above.[10,12] The results from diluted CRMs using three different matrices underpin this, as shown in Figure 3. Previously, Li et al. proved the feasibility of pure water in insulin dilution, but the results were for high-insulin serum samples, not for insulin in buffer solution.[27] Indeed, while previous investigations have proposed serum matrix reference materials for insulin assays, no CRM with complete metrological traceability to SI is commercially available to date.[28,29]

4 | CONCLUSIONS

Based on the results, we clarify the issues and suggest future tasks for standardization from the point of view of metrology as follows. Each insulin result should clearly state its analysis method, measurement traceability, and any conversion factor used in the post-analysis step. Ultimately, SI-unit-based WHO ISs may help to easily establish wider standardization, and a sole conversion factor should be chosen and applied upon universal consensus. Likewise, the development of matrix matched CRMs commutable to different immunoassay methods within meaningful clinical ranges will improve the comparability of insulin analysis. The ultimate goal of standardization is demonstrated by a well-defined reference standard together with a reference measurement system. Therefore, we believe that the discussed points in this study can be major factors for assessment of results comparability in protein analysis particularly with similar case as insulin, which has various types of quantification methods and notably in this study includes immunoassays.

ACKNOWLEDGMENTS

This research was supported by the project "Establishment of Measurement Standards for Bio-Diagnostic Analysis" (KRISS 22011067), funded by the Korea Research Institute of Standards and Science.

CONFLICT OF INTEREST

Authors state no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included in the manuscript and the Supporting Information of this article.

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SUPPORTING INFORMATION

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How to cite this article: Rosli N, Kwon H-J, Lim J, Yoon YA, Jeong J-S. Measurement comparability of insulin assays using conventional immunoassay kits. *J Clin Lab Anal*. 2022;36:e24521. doi: 10.1002/jcla.24521