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Original Article

Comparative analysis of reliability and validity of six glucometers according to hematocrit based on ISO guidelines

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Abstract: The management of diabetes using different methods such as diet, exercise, and medical treatment can delay the progression of diabetes and its complications. Complications of diabetes can be reduced by the careful regulation of blood glucose. Self-monitoring blood glucose enables diabetes patients to control their blood glucose levels effectively and is used globally to manage diabetes, indicating the importance of blood glucose testing. ISO 15197:2013 is an international regulation for verifying the reliability and validity of glucometers. Here, we evaluated six glucometers that were purchased randomly on the Korean market using the following verification criteria: precision evaluation, accuracy evaluation, and effect of hematocrit concentration. All verifications were performed according to ISO 15197:2013. In a repeatability study, the range for the total coefficient of variation was 1.3-4.3%, 1.5-5.7%, and 1.4-3.4%, respectively. In the intermediate precision evaluation, the coefficient of variation was 1.6-6.6%, 2.5-6.8%, and 1.1-3.3% for the three levels of control specimen (51-110, 151-250, 251-400 mg/dL), respectively. Three glucometers met ISO 15197:2013 for the accuracy criteria, and only one glucometer met the ISO 15197 hematocrit effect. More than 80% of the evaluated glucometers did not fulfill the ISO 15197:2013 criteria, and most were affected by the hematocrit concentration. These inaccurate results can increase the risk of uncontrolled blood glucose levels in diabetes patients, who should consider these limiting functions when evaluating their results. As venous blood was used in this study, further evaluations will be needed to confirm the results using capillary blood.

Keywords: Glucometer, reliability, validity, ISO guidelines

Introduction

The prevalence of diabetes mellitus (DM) is greatly increasing, and the number of patients suffering from this disease is estimated to reach around 415 million (415,000,000) by 2015 [1]. The number of diabetes patients is rapidly increasing particularly due to the aging society and lifestyle changes, and the prevalence of DM in Korea has also increased 5- to 6-fold from approximately 1.5% to 7-9% in the last 30 years [2]. Thus, DM is becoming a worldwide social issue. It has been proven recently that blood glucose control and blood pressure control along with various treatment methods can reduce acute complications and the progression of disease in types 1 and 2 diabetes [3]. Blood glucose levels can be managed by different ways such as diet, exercise, and medical treatment. The most important factor is for the patient to manage the disease by being aware of his/her own fluctuating blood glucose levels through self-measurement and motivated regarding the necessity of self-control. As a result, the disease can be better controlled, and progression to diabetic retinopathy, neuropathy, nephropathy, and other complications can be prevented [4, 5]. The accuracy of glucometers is very important because their function has a direct effect on the control of blood glucose levels such as the determining the dosage of insulin [6].

The American Diabetes Association recommends the auto-measurement of blood glucose in the following cases: 1) patient groups receiving intense insulin therapy should measure blood glucose levels at least four times a day, as less frequent measurements could lead to failure of blood glucose control, 2) to diagnose and prevent hypoglycemia in patients without symptoms or unnoticeable initial danger signs,

3) to avoid severe hyperglycemia caused by using medications that can affect the secretion or function of insulin, or by being at increased risk such as in comorbidities and aging, 4) to control medications according to lifestyle modifications such as exercise or change in diet, and 5) to inform the decision regarding the need to initiate insulin treatment in gestational diabetes [3].

The International Organization for Standardization (ISO) 15197:2013, which is an international standard set to evaluate the function of glucometers, states that the product should satisfy at least two of the accuracy parameters. The first parameter indicates that for glucose levels less than 100 mg/dL, 95% of results should be within ±15 mg/dL of laboratory values, and for levels greater than 100 mg/dL, 95% of results should be within the % bias ±15% compared to the index value. The second parameter is described as all measurements reaching 99% of Zone A and Zone B of the Consensus Error Grid (CEG) [7].

In Korea, the current domestic glucose meter market share is almost 86 million dollars based on production and import/export per product, with 16.1% growth per year on average within the last 5 years. There are 16 domestic corporations and approximately 13 overseas corporations in the domestic market [8].

In this study, we randomly purchased six glucometers currently being sold on the domestic market and evaluated their general functions. Glucometers can be categorized into two types. The first is the electrochemical type, which quantitatively measures the electrons being generated by using electrodes when glucose is oxidized into hydrogen peroxide or oxidized medium and then returns to its original oxidized form; the second is the spectrometric type, which quantitatively measures reflectance and penetrance by using a spectrometer to measure the degree of change in color using a chromogen (H_2O_2) that causes a color change when glucose is oxidized.

Most international glucometers are the electrochemical type and use glucose oxidase (GOX) as the reaction enzyme. GOX acquires electrons by oxidizing glucose, which can be affected by blood oxygen levels; thus, glucose level measurements can only be performed through capillaries. However, a product that uses glucose dehydrogenase (GDH), which is unaffected by blood oxygen levels, has been introduced recently. A large advantage of using GDH is that it is not influenced by blood oxygen levels, as it acquires electrons by isolating hydrogen from glucose; therefore, it can measure blood glucose in a capillary, vein, or artery. This study did not recruit subjects and instead used remaining venous blood scheduled to be discarded after regular checkups, and all six types of tested glucometers used the glucose dehydrogenase flavin adenine dinucleotide (GDH-FAD) enzyme.

Materials and methods

Products and samples

In this study, we evaluated the precision, accuracy, and interference effect of hematocrit of six glucometers being sold domestically. The products were labeled as A, B, C, D, E, and F companies. All six types of glucometers were products that measure blood glucose levels using venous blood samples, as they use the GDH-FAD enzyme.

Precision was evaluated by two methods, repeatability and intermediate precision, according to the ISO 15197:2013 guideline.

All experiments necessary for the study used remaining blood that was to be discarded after HbA1c tests were performed for patients who had visited the endocrinology department of a general hospital in Anyang, Korea. All concentration measurements and number of samples were evaluated by calculation according to the ISO 15197:2013 guideline.

Because we used remaining blood samples that were to be discarded, we may be exempt from informed consent. This study received approval from the Institutional Review Board of the Catholic University of Korea (IRB approval number: MC16OASI0052).

Evaluation

All measurements were taken following the ISO 15197:2013 guideline, with all strips used in the experiment being from a single lot. The quality control of the evaluated glucometers and strip storage followed the recommendations of each manufacturer.

Table 1. Precision results of glucometers

Glucometers		Repeatability			Intermediate precision		
		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
A	Mean (mg/dL)	132	245	418	84	255	355
	SD (mg/dL)	2.9	4.6	6.9	3.1	7.8	11.6
	CV (%)	2.2	1.5	1.6	3.7	3.1	3.3
B	Mean (mg/dL)	107	252	343	77	232	306
	SD (mg/dL)	4.5	11.0	11.6	5.1	15.9	8.1
	CV (%)	4.2	4.4	3.4	6.6	6.8	2.7
C	Mean (mg/dL)	119	257	358	73	228	313
	SD (mg/dL)	4.5	8.8	5.0	1.2	5.8	3.4
	CV (%)	3.8	3.4	1.4	1.6	2.5	1.1
D	Mean (mg/dL)	135	311	438	77	236	354
	SD (mg/dL)	2.5	5.6	6.9	1.3	6.6	9.2
	CV (%)	1.8	1.8	1.6	1.7	2.8	2.6
E	Mean (mg/dL)	131	280	401	58	260	376
	SD (mg/dL)	3.2	15.8	12.8	1.1	11.0	10.9
	CV (%)	2.4	5.7	3.2	1.8	4.2	2.9
	Mean (mg/dL)	130	294	412	57	214	326
F	SD (mg/dL)	5.7	5.3	9.4	2.9	7.0	6.5
	CV (%)	4.4	1.8	2.3	5.2	3.2	2.0

Abbreviations: SD, Standard Deviation; CV, Coefficient of Variation.

Remnant blood samples slated for disposal were used as specimens for reproducibility evaluation. Three different concentrations of specimen (51-110, 151-250, 251-400 mg/dL) were used as per the ISO 15197:2013 guideline. Glycolysis was performed to produce a low-glucose specimen, and 20,000 mg/dL Glucose D-stick solution (Sigma, USA) was used to produce a high-glucose specimen of a desired concentration. Each specimen was measured 20 times per device in order to evaluate the precision, and interim precision was evaluated by creating three specimens (51-110, 151-250, 251-400 mg/dL) with PBS (phosphate buffer saline) and 40,000 mg/dL Glucose D-stick solution and taking measurements twice daily for 10 d in total.

The accuracy of the six different blood glucose monitors was evaluated using 100 remnant blood samples as per ISO 15197:2013. Six venous blood samples slated for disposal were randomly selected per each blood glucose monitor, and the samples were measured continuously using a pipette. Immediately after the measurement of the blood glucose level, the samples were centrifuged for 10 min at 2,000× *g*, and two consecutive measurements of plasma glucose were obtained using an automated chemical analyzer (Roche Cobas 600; Roche diagnostic GmbH). The automated chemical analyzer used in this evaluation is a central laboratory biochemical device that uses hexokinase, a reference method for blood glucose measurement, to measure the plasma glucose level.

The measured values of each blood glucose monitor were compared to the reference blood glucose level and subjected to relativity analysis through simple regression analysis, and 95% confidence intervals were obtained. Furthermore, measurement error was obtained using the CLSI EP09-A2:2004 method with comparison and bias estimating using patient samples [9].

Blood samples were manipulated by adding or removing plasma to achieve five hematocrit intervals (20±2%, 30±2%, 40±2%, 50±2%, 60±2%), as per ISO 15197:2013. Each sample was again manipulated by adding or removing glucose to produce three different glucose concentrations per sample, for a total of 15 samples.

Statistical analysis

Microsoft Excel 2010 (Microsoft, NY, USA) software was used for all statistical analyses. The measurements from the blood glucose monitors were compared and analyzed using the mean of two measurements from the automated chemical analyzer as the reference value, and values outside a measurement error of ±4 mg/dL for blood glucose levels greater than 100 mg/dL and those outside a measurement error of ±4% for blood glucose levels less than 100 mg/dL were excluded from statistical analysis. In addition, accuracy was evaluated according to the following standards, as indi-

Table 2. Accuracy results of glucometers

Glucometer	ISO 15197:2013		Number		
	Requirements fulfilled	Percentage	Within ±5 mg/dL or ±5%	Within ±10 mg/dL or ±10%	Within ±15 mg/dL or ±15%
A	Yes	98% (98/100)	48% (48/100)	88% (88/100)	98% (98/100)
B	No	76% (76/100)	17% (17/100)	47% (47/100)	76% (76/100)
C	No	74% (63/100)	10% (10/100)	31% (31/100)	74% (74/100)
D	Yes	97% (97/100)	56% (56/100)	88% (88/100)	97% (97/100)
E	Yes	95% (92/100)	35% (35/100)	76% (76/100)	95% (95/100)
F	No	86% (86/100)	38% (38/100)	71% (71/100)	90% (90/100)

cated by ISO/DIS 15197:2013: ≥95% of measurements falling within ±15 mg/dL of the standard value difference if the standard value of blood glucose level is <100 mg/dL, ≥95% of measurements falling within ±15% of %Bias if the standard value to blood glucose level is ≥100 mg/dL, and ≥95% of total standard values satisfying these criteria. Error grid analysis to evaluate clinical accuracy was also performed, and five areas (A, B, C, D, E) of a consensus error grid were marked.

The representative value of a sample was designated as the mean of five measurements per concentration, and hematocrit interference was evaluated by obtaining the measurement error of each sample with a measured value of 40±2% as the standard hematocrit value.

Results

The distribution of the repetitive coefficient of variation of the six glucometers was 1.8-4.4% at Level 1, 1.5-5.7% at Level 2, and 1.4-3.4% at Level 3. The distributions of the coefficient of variation of intermediate precision were 1.6-6.6%, 2.5-6.8%, and 1.1-3.3% at Levels 1, 2, and 3, respectively (**Table 1**). As there is no protocol for precision that satisfies the standard in ISO 15197:2013, we applied the standards set by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which is a standard of quality for the accuracy and reliability of testing equipment. All product values met the coefficient of variation within 10% of the precision criteria of CLIA'88 [10].

Accuracy was evaluated according to the accepted standards of the ISO 15197:2013 guideline. Of the six glucometers, only the A, D, and E products met the accuracy acceptance criteria of the ISO 15197:2013 guideline, at values of 98.0%, 96.0%, and 95.0%, respectively (**Table 2**). The Diff & %Bias plot of each glucometer is as shown in (**Figure 1**). Most glucometers showed a tendency towards a negative error range compared to the standard, possibly because of measurement deviations among the unique standard measurement equipment used by the manufacturers. In our study, we used Cobas equipment with the hexokinase method for evaluation, but many manufacturers use the YSI 2300 STAT (YSI Life Sciences, Yellow springs, USA) with the glucose oxidase method as the equipment for the standard measurement. According to Freckmann, MD of the Institut für Diabetes-Technologie Forschungs-und Entwicklungsgesellschaft mbH, Ulm in Germany, there is a difference between these two pieces of equipment that affects the results of glucometer evaluation [11].

The correlation between the six glucometers and the standard values showed an excellent correlation of more than 0.95 according to linear regression analysis (**Table 3**).

A consensus error grid analysis was performed on the basis of the measurement results used in the accuracy evaluation (**Table 4**). Product D showed excellent results, as all measurements were within the A area and satisfied the permissible standard that more than 99% of the measurement values should be in the A or B areas (**Figure 2**).

According to the ISO 151597:2013 guideline, the deviation due to hematocrit should be less than ±0.56 mmol/L (±10 mg/dL) for glucose concentrations less than 5.55 mmol/L (100 mg/dL, and less than ±10% for glucose concentrations greater than or equal to 5.55 mmol/L (100 mg/dL). Product E was the only one that satisfied this criterion for the permis-

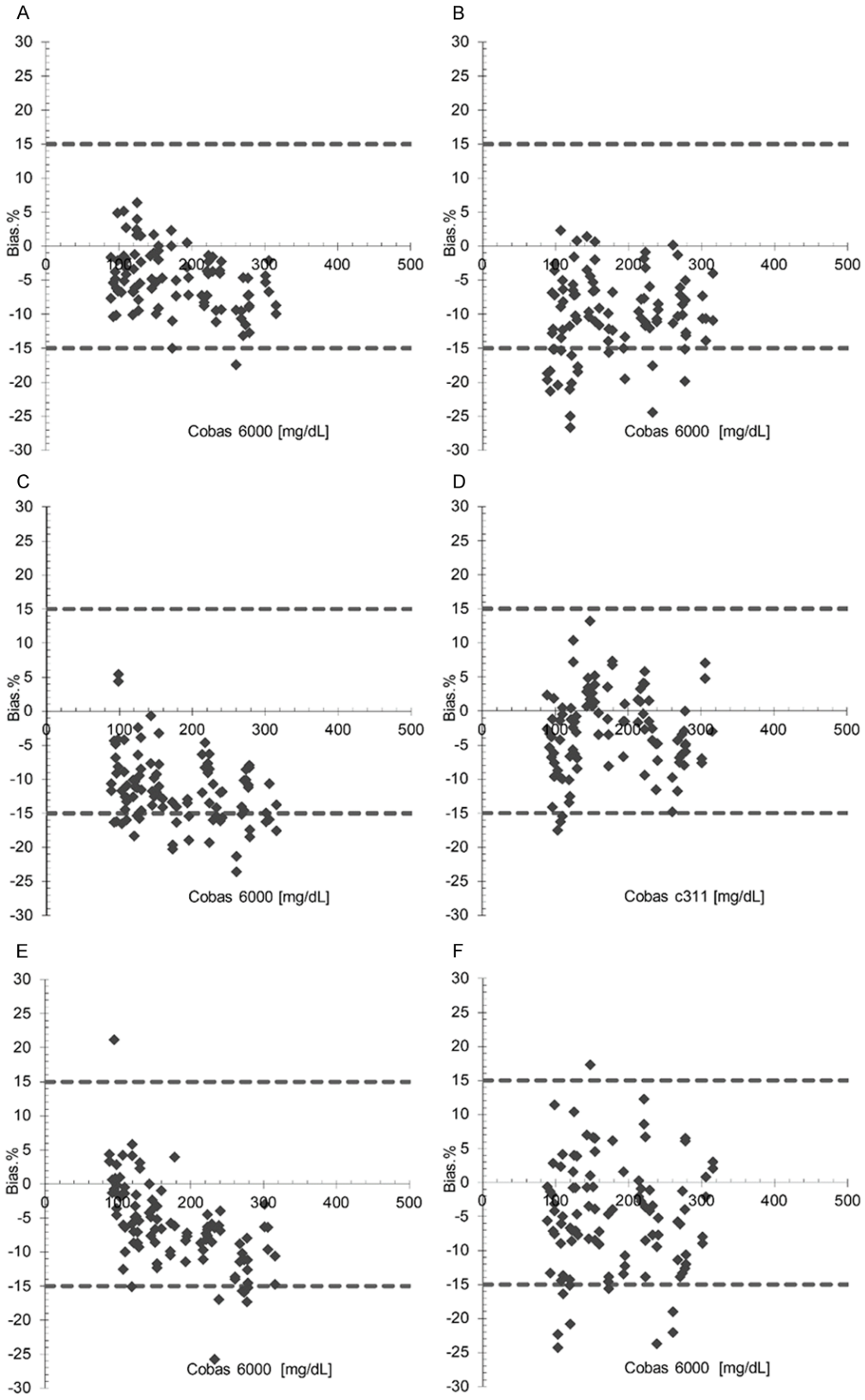
A
B
C
D
E
F
Bias.%
Cobas 6000 [mg/dL]
Cobas c311 [mg/dL]

Figure 1. Difference and bias (%) plot of glucometers. The relative differences in percentage between an individual result of a glucometer and the corresponding result of the reference method were plotted against the average of the result of the glucometer and the corresponding result of the reference method.

Table 3. Linear regression between glucometers and Cobas 6000

Glucometer	Linear regression	95% CI Slope	95% CI Intercept	R^2	N
A	y=0.8945x+8.7457	(0.8721, 0.9167)	(4.4883, 13.0032)	0.9848	100
B	y=0.9164x-3.2209	(0.8861, 0.9466)	(-8.9984, 2.5566)	0.9736	100
C	y=0.8397x+6.6444	(0.8154, 0.8640)	(2.0128, 11.2760)	0.9797	100
D	y=0.9625x+1.5584	(0.9315, 0.9935)	(-4.3676, 7.4845)	0.9748	100
E	y=0.8344x+16.0890	(0.8090, 0.8597)	(11.2494, 20.9285)	0.9776	100
F	y=0.9413x+1.3962	(0.8963, 0.9864)	(-7.2111, 10.0037)	0.9726	100

Table 4. Consensus error grid analysis of glucose levels measured by glucometers against Cobas 6000

Glucometer	Consensus Error Grid zone				
	Zone A	Zone B	Zone C	Zone D	Zone E
A	98/100 (98%)	2/100 (2%)	0/100 (0%)	0/100 (0%)	0/100 (0%)
B	95/100 (95%)	5/100 (5%)	0/100 (0%)	0/100 (0%)	0/100 (0%)
C	94/100 (94%)	5/100 (5%)	0/100 (0%)	0/100 (0%)	0/100 (0%)
D	100/100 (100%)	0/100 (0%)	0/100 (0%)	0/100 (0%)	0/100 (0%)
E	95/100 (95%)	5/100 (5%)	0/100 (0%)	0/100 (0%)	0/100 (0%)
F	97/100 (97%)	3/100 (3%)	0/100 (0%)	0/100 (0%)	0/100 (0%)

sible range according to hematocrit and glucose concentration levels, and the products showed variable deviation ranges depending on the different manufacturers. Manufacturer E had the best function, with a deviation range of -3.9-3.4%, and manufacturer F was affected the most by the interference, with a deviation range of maximum -40-45% (**Figure 3**).

Discussion

The differences in function between various glucometers from different companies were clearly defined, and the products did not satisfactorily meet all the performance standards that at the manufacturers claimed. However, this study was a single institution study, and because of the limitation that the study could not be standardized regarding all conditions for each manufacturer at the time each product was made, it is difficult to state that they did not meet the accuracy requirements of ISO 15197:2013. However, these results are valuable as a reference for the evaluation of the function of glucometers, as blood glucose levels for patient checkups are currently measured using the hexokinase method in most hospitals. Nevertheless, there was a wide gap in function regarding hematocrit and accuracy evaluation (especially hematocrit), which are not influenced by the standard value.

The glucose levels in the intercellular space between plasma and blood cells are equal, but as one-third of the space in blood cells is taken up by hemoglobin and as hemoglobin uses glucose as an energy source, whole blood that includes blood cells has a lower glucose level than plasma. Therefore, as lower hematocrits contain more plasma, the glucose level is perceived as higher than actual levels, and higher hematocrits result in glucose levels that are lower than actual levels, as it contains more blood cells. To address this issue, each glucose meter applies a unique algorithm depending on the manufacturer to minimize the effect of hematocrit on the measurements, and most products state that the products guarantee 20-60% or 10-70% of the hematocrit. The importance of the effect of hematocrit on glucometers is that their use is not limited to just diabetic patients, as they are also used for neo-

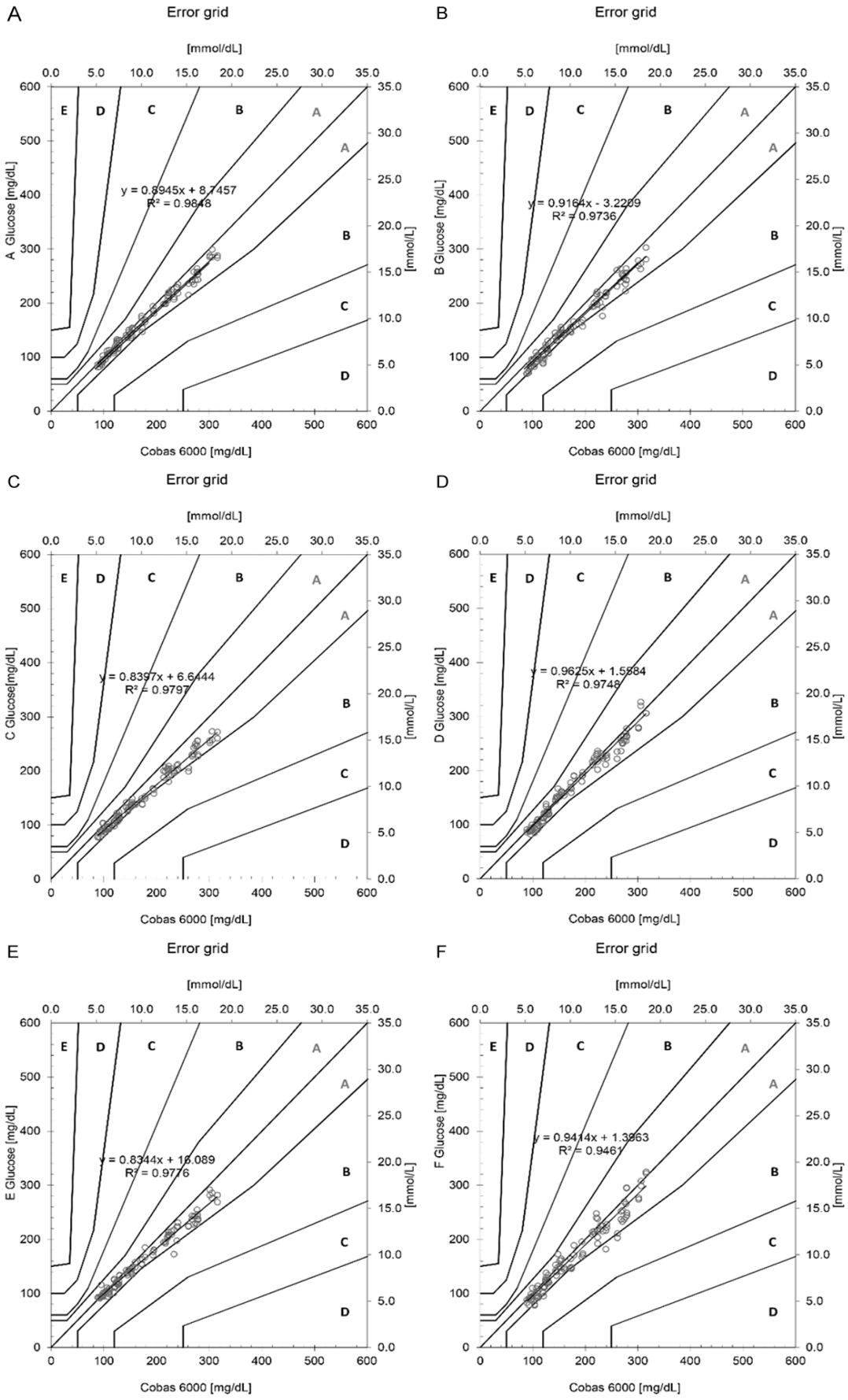
A
Error grid
[mmol/dL]
A Glucose [mg/dL]
y = 0.8945x + 8.7457
R² = 0.9848
Cobas 6000 [mg/dL]
[mmol/L]
B
Error grid
[mmol/dL]
B Glucose [mg/dL]
y = 0.9164x - 3.2269
R² = 0.9736
Cobas 6000 [mg/dL]
[mmol/L]
C
Error grid
[mmol/dL]
C Glucose[mg/dL]
y = 0.8397x + 6.6444
R² = 0.9797
Cobas 6000 [mg/dL]
[mmol/L]
D
Error grid
[mmol/dL]
D Glucose [mg/dL]
y = 0.9625x + 1.5884
R² = 0.9748
Cobas 6000 [mg/dL]
[mmol/L]
E
Error grid
[mmol/dL]
E Glucose [mg/dL]
y = 0.8344x + 16.089
R² = 0.9776
Cobas 6000 [mg/dL]
[mmol/L]
F
Error grid
[mmol/dL]
F Glucose [mg/dL]
y = 0.9414x + 1.3863
R² = 0.9461
Cobas 6000 [mg/dL]
[mmol/L]

Figure 2. Consensus error grid analysis of capillary blood glucose results. Each specimen was measured in duplicate by each method. Zone A, clinical accurate (no effect on clinical action); Zone B, clinically acceptable (altered clinical action-little or no effect on clinical outcome); Zone C, altered clinical action-likely to affect clinical outcome; Zone D, altered clinical action having a significant medical risk; and Zone E, altered clinical action having dangerous consequences.

nates with high hematocrits and pregnant women with low hematocrits.

Patients with diabetes often have comorbid conditions such as renal damage and reduced renal function and anemia resulting from different unexplained pathophysiologies. Moreover, in their study on diabetes patients visiting the Jeonbuk University Hospital, Jin *et al.* reported that the average hematocrit of 78 patients without peripheral neuropathy was 32.0±4.3, whereas the average hematocrit of 76 patients with peripheral neuropathy was 30.9±3.4 [12]. In addition, a domestic study performed by Kim *et al.* on 77 diabetic nephropathy patients with chronic renal disease reported an average hematocrit of 25.2±4.5 [13].

Patients with diabetes have relatively lower hematocrit levels compared to those of healthy individuals, and these patients may either accurately measure their level or obtain a false positive result that is 45% higher than their actual blood glucose level depending on the glucose meter product that they use. This discrepancy will likely adversely affect glucose level control and prescription of medication by the medical staff.

Of the many physical changes appearing during pregnancy, the plasma volume starts to increase during the 10th week and increases up to 50% of the levels at the time of fertilization at around the 34th week. Erythrocytes increase as a result of erythropoiesis, but as the numbers do not increase relative to the extent of plasma volume expansion, hemoglobin or hematocrit decreases. You *et al.* performed a cross-sectional study on the biochemical iron analysis and iron deficiency states of 209 healthy pregnant women without diabetes, heart disease, or renal disease who were receiving prenatal checkups at the Woolsan Community Health Center. The hematocrit distribution was 36.1±2.9 during the early stages of pregnancy, 33.1±2.6 during the middle stages, and 34.8±3.5 during the late stages, with 2% of the pregnant women having a hematocrit of 25.0-27.5 [14].

Gestational diabetes is diagnosed using a 50 g glucose tolerance test at 24-28 weeks of pregnancy, and a glucose level exceeding 140 mg/dL after 1 h is further tested using a 100 g glucose tolerance test, in which levels exceeding 180 mg/dL after 1 h, 155 mg/dL after 2 h, and 140 mg/dL after 3 h confirm the diagnosis [15]. Most primary ob-gyn clinics excluding secondary, tertiary, and general hospitals use glucometers to measure blood glucose levels in pregnant women as they do not require large biochemical equipment, and the interference effect depending on the hematocrit of the glucometers could be a risk factor similar to a misdiagnosis.

Neonates continually receive a steady supply of glucose through the maternal placenta, and very rarely experience transient hypoglycemia due to an intermittent supply of glucose through food after birth. However, persistent or recurring hypoglycemia may cause neurological sequelae; therefore, glucose monitoring is necessary. Glucose monitoring should be performed within 1-2 h after birth or every time symptoms matching hypoglycemia are observed, and most newborn units use an on-site glucose meter to measure blood glucose levels, as it is the fastest method [16, 17].

According to a neonatal hematocrit study performed on 41,957 neonates in a U.S. Multihospital Health Care System, the change in hematocrit from day 1 to 28 after birth was 68%, up to a level of 48% [18]. Because of the interference effect, using glucose meter for monitoring neonatal blood glucose levels was concluded to pose a significant risk.

Glucometers, which are on-site exam equipment, have the advantage of reducing the time needed to make decisions, as they are quick and easy to use, but the results of this study indicate that their function is affected by the actual checkup environment and numerous variation factors.

The ISO 15197:2013 regulations have been required in European nations since 2016, and

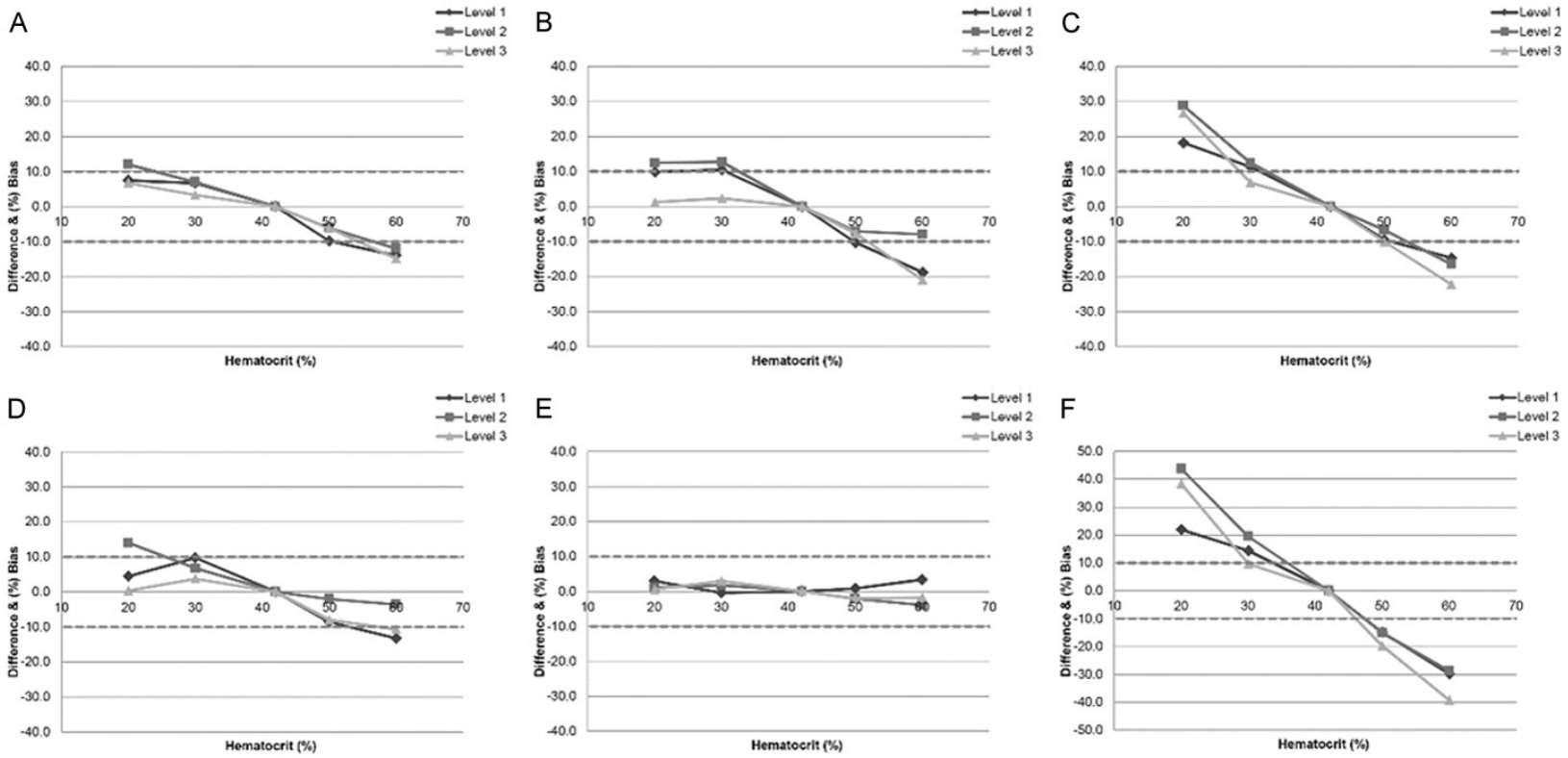

Figure 3. Interference of the hematocrit in glucometers. The x-axis shows the hematocrit (%) for each sample. The y-axis shows the bias that calculated glucose of each hematocrit by standard glucose of 42% hematocrit.

only products that have been officially confirmed regarding accuracy and hematocrit by undergoing clinical studies are approved and allowed to be sold; moreover, there are also professional clinical testing facilities for glucometers. However, in Korea, the regulations for authorizing the sale and approval of glucometers are not clearly established, but awareness is also low.

The limitations of this study included that we used leftover venous blood sample, whereas most glucometers directly use capillary blood rather than venous blood. Further studies that perform accuracy evaluations using capillary blood and evaluate interference when using capillary hematocrit with recruited subjects are necessary.

More than 80% of the evaluated glucometers did not fulfill the ISO 15197:2013 criteria, and most were affected by the hematocrit concentration. These inaccurate results can increase the risk of uncontrolled blood glucose levels in diabetes patients, who should consider these limiting functions when evaluating their results. As venous blood was used in this study, further evaluations will be needed to confirm the results using capillary blood.

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Disclosure of conflict of interest

None.

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