

Performance Evaluation of the GlucoDr Plus Glucometer

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Abstract

Background: Because strict glucose control is important for reducing the complications of diabetes, the self-monitoring of blood glucose is one of the fundamental treatment modalities. Many glucometers have been developed. In the present study, we evaluated a new glucometer: GlucoDr™ Plus (Allmedicus, Anyang, Gyeonggi-do, Republic of Korea).

Methods: The evaluation was performed based on Clinical and Laboratory Standards Institute guidelines. Interferences by ascorbic acid, uric acid, maltose, and acetaminophen were examined, and the performance of the unit was compared to those of six other glucometers. The effects of hematocrit, of oxygen partial pressure (PaO₂), and of multiple users were also evaluated.

Results: Within-run, between-run, between-day, and total imprecision (coefficients of variation) were 0.99–4.98%. Satisfactory linearity was found for glucose concentrations of 32.5–786.5 mg/dL ($R^2 = 0.9985$). A comparison with the reference laboratory method showed close concordance over the entire range of concentrations evaluated ($R^2 = 0.9869$). No significant effects were noted due to added interferents, hematocrit, and PaO₂.

Conclusions: The GlucoDr Plus showed acceptable performance in terms of precision and linearity. It was minimally affected by various interferents. GlucoDr Plus is suitable for the self-monitoring of blood glucose by patients with diabetes.

Introduction

DIABETES MELLITUS is a metabolic disease that develops because of derangement of an individual's capacity to control blood glucose. In 2000, the number of patients with diabetes worldwide was estimated to be approximately 171 million, and this figure is expected to increase to 366 million in 2030.¹ The discovery that strict blood glucose control is more helpful than relieving the symptoms of diabetes in terms of preventing complications represented a sentinel point in the treatment of diabetes.^{2,3} To achieve a good blood glucose control, patients should constantly check their blood glucose levels, and thus a portable glucometer is an essential device.

There are two types of glucometers, which rely on different signal detection principles, i.e., spectroscopic and electrochemical meters. When using spectroscopic meters, the amount of blood sample introduced to the response layer depends on the amount of blood loaded, which leads to measurement errors, and thus electrochemical meters are more widely used today. Methods of measuring blood glucose are classified according to the enzyme and coenzyme used, for example, the glucose oxidase method, the glucose dehydrogenase-based NAD method, the glucose dehydrogenase-based pyrroloqui-

noline quinone method, the glucose dehydrogenase-based flavin adenine dinucleotide (FAD) method, the glucose hexokinase method, and others. Of these, the glucose oxidase method is most widely used. However, this method requires oxygen to convert glucose into gluconolactone, which can result in spuriously elevated values when oxygen contents are high in capillary or arterial blood.⁴ This problem can be overcome by using glucose dehydrogenase, which is not affected by oxygen content. However, the glucose dehydrogenase-based pyrroloquinoline quinone method is subject to interference by sugars other than glucose.⁵

In the present study, we evaluated the performance of a new glucometer, GlucoDr™ Plus (Allmedicus, Anyang, Gyeonggi-do, Republic of Korea), which utilizes a glucose dehydrogenase-based FAD method. We compared its performance with those of widely used glucometers.

Materials and Methods

Glucometer

The GlucoDr Plus is an electrochemical glucometer based on the glucose dehydrogenase method and displays blood glucose levels based on electric current generated by a

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reaction between an enzyme immobilized on an electrode and glucose in blood. The system uses FAD-glucose dehydrogenase, which minimizes the effects of oxygen as well as sugars other than glucose. Gold is used for electrodes because of its noble nature and its high conductivity.

Precision

Three control solutions and five venous EDTA-treated whole blood samples were used to evaluate precision. Control solutions were measured twice a day for 20 days, as recommended by the Clinical Laboratory Standards Institute (CLSI), and within-run, between-run, between-day, and total imprecisions were calculated.⁶ Within-run imprecision in patient samples was assessed using 12 consecutive measurements of venous whole blood samples at five different concentrations.

Linearity

Two venous whole blood samples with glucose concentrations of 32.5 and 786.5 mg/dL were used, as recommended by the CLSI.⁷ The two samples were mixed in volume ratios of 4:0, 3:1, 2:2, 1:3, and 0:4 to produce five samples with different concentrations. Each sample was measured four times.

Effect of hematocrit

Twenty-one whole venous blood EDTA samples with hematocrit values of 12.1–58.0% were selected and measured with GlucoDr Plus. For each sample, plasma glucose concentrations were measured using an automated chemistry analyzer (model 200FR, Toshiba, Tokyo, Japan), and hematocrit effects were evaluated by calculating the ratio of glucose values measured by the glucometer and the automated chemistry analyzer.

Interference

Two venous whole blood EDTA-treated samples with different glucose concentrations were selected and measured five times with GlucoDr Plus to determine glucose concentrations before adding interferents. Low and high concentrations of ascorbic acid (3.5 and 6 mg/dL), acetaminophen (3 and 8 mg/dL), uric acid (7 and 25 mg/dL), and maltose (10 and 200 mg/dL) were then mixed with samples, and glucose concentrations were measured. The glucose concentrations determined before and after adding the interferents were compared.⁸

Comparison with other glucometers and the automated chemistry analyzer

One hundred twenty venous whole blood EDTA-treated samples with glucose concentrations in the range 33–327 mg/dL were randomly selected and tested using GlucoDr Plus and six other glucometers: Accu-Chek® (Roche Korea, Seoul, Republic of Korea), OneTouch® Ultra® (LifeScan Korea, Seoul), Optium™ Xceed (Abbott Korea, Seoul), Mirae 3.3G (Infopia, Anyang), Gluchec (KMH, Anyang), and MWD Pen Sensor (MedWatchDoc GmbH & Co., Lüneburg, Germany). All tests were performed twice, and results were evaluated according to the CLSI guidelines.⁹

Test strip stability

Three control solutions were measured using GlucoDr Plus immediately and 1, 3, and 7 days after opening the test strip container. All tests were performed three times, and average values were compared.

Effect of multiple users

Three inexperienced persons were trained to operate GlucoDr Plus just prior to testing. Each person measured three control samples independently.

Effect of oxygen partial pressure (PaO₂)

One hundred arterial whole blood heparinized samples with PaO₂ values of 51.6–189.4 mm Hg were randomly selected. Each sample was measured twice using GlucoDr Plus. Their plasma glucose concentrations were also measured twice using an automated chemistry analyzer. The effect of PaO₂ was evaluated by calculating the ratio of glucose values measured by the automated chemistry analyzer and the glucometer.

Statistics

All statistical analyses were performed using Excel 2003 (Microsoft Corp., Redmond, WA) and SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL). A correlation equation and Pearson's correlation coefficient (R^2) were obtained during the correlation analysis. Clarke error grid analysis was performed to evaluate the clinical performance of the glucometer. Values of $P < 0.05$ were deemed significant.

Results

Precision

Coefficients of variation (CVs) of within-run, between-runs, between-days, and total imprecisions using the control solutions were 1.5–2.2%, 1.7–3.9%, 1.0–2.3%, and 2.6–5.0%, respectively (Table 1). CVs of with-run imprecisions using venous whole blood samples for glucose concentrations ranged from 1.3% to 5.0% (Table 1). GlucoDr Plus showed an acceptable range of imprecision that nearly meets the requirements for glucose measurements.^{10,11}

Linearity

GlucoDr Plus showed acceptable linearity in the range 32.5–786.5 mg/dL (Fig. 1). The coefficient of determination was 0.998, and the slope and intercept were 1 and 0, respectively.

Effect of hematocrit

To evaluate the effect of hematocrit, 21 samples with a hematocrit of 12.1–58.0% and glucose concentrations in the range 57.5–369.5 mg/dL were used. Most of the values measured by GlucoDr Plus were slightly lower than those from the Toshiba 200-FR with minor exceptions. Glucose values obtained using GlucoDr Plus were different by –10.9 mg/dL and –7.1% on average. However, as shown in Figure 2, glucose values measured with GlucoDr Plus were not significantly affected by hematocrit ($R^2 = 0.0437$, $P = 0.965$).

TABLE 1. IMPRECISION OF GLUCODR PLUS

	At mean glucose concentration (mg/dL)				
	Level 1 (44.3)	Level 2 (128.1)	Level 3 (365.6)		
Control solutions					
Within-run imprecision (%)	1.5	2.0	2.2		
Between-run imprecision (%)	1.7	3.9	3.2		
Between-day imprecision (%)	1.0	2.3	1.0		
Within-device imprecision (%)	2.6	5.0	4.1		
	Level 1 (33.4)	Level 2 (95.8)	Level 3 (136.4)	Level 4 (204.9)	Level 5 (289.4)
Patient samples					
Within-run imprecision (%)	5.0	1.3	2.7	3.0	2.1

Imprecision (%) is defined as CV.

Interference

Table 2 shows changes in measured glucose values after adding low or high concentrations of ascorbic acid, uric acid, maltose, or acetaminophen. No significant interference was observed from the four interferences tested. A degree of positive interference was found for ascorbic acid, up to about 10% of the initial glucose concentration. Interferences caused by uric acid, maltose, and acetaminophen at the difference glucose concentration were negligible.

Comparison with the automated chemistry analyzer

Correlations between the automated chemistry analyzer and the GlucoDr Plus and the six glucometers are shown in Table 3. All seven glucometers showed acceptable correlations ($R^2 = 0.9643-0.993$). In terms of Clarke error grid analysis, all values were distributed in zone A (Fig. 3).

Test strip stability

Test strips were stable for 7 days after exposed to ambient environment. The average difference between glucose values after 7 days was within $\pm 3.4\%$ of values obtained immediately after opening (Fig. 4). The differences at low and high concentrations were statistically significant ($P < 0.01$) but clinically insignificant (44.8–48.2 mg/dL at low concentration and 400.8–410.0 mg/dL at high concentration). The difference at the middle concentration was statistically and clinically insignificant ($P = 0.271$, 127.6–132.2 mg/dL).

Effect of multiple users

The CVs of glucose values measured by individual users were 4.7–6.3%, 1.7–2.9%, and 2.5–2.8% for low, middle, and high concentration control solutions. Average values measured by the three users differed significantly at low concentration

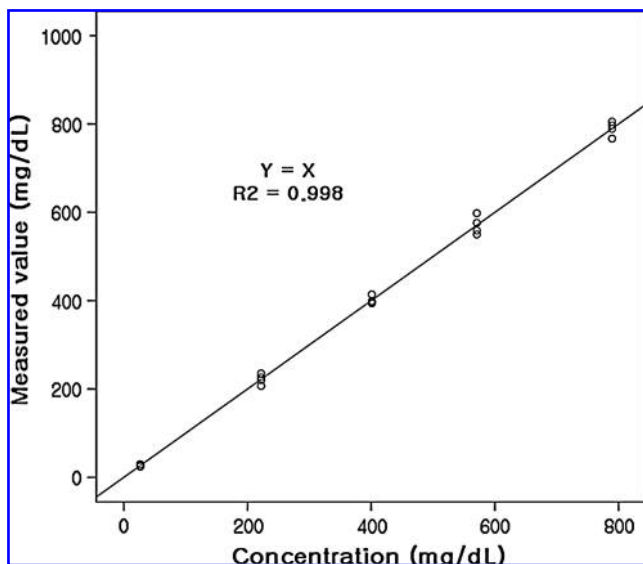


FIG. 1. Linearity of GlucoDr Plus measurements. The x-axis represents the expected value of glucose concentrations, and the y-axis represents measured values generated by the glucometer.

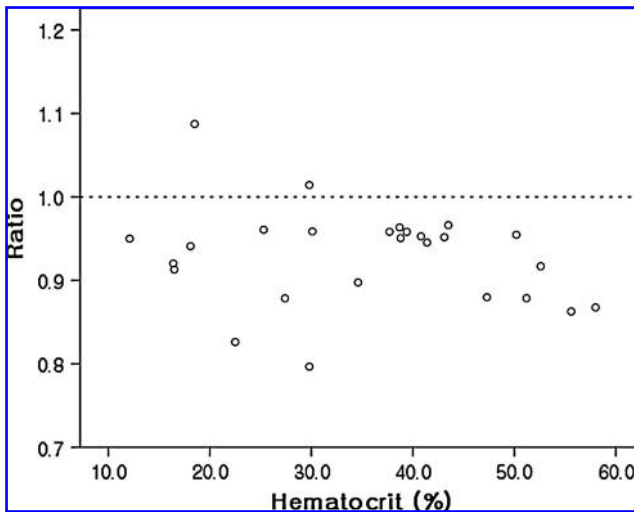


FIG. 2. Effect of hematocrit. The ratio was calculated as the glucose level resulted from the GlucoDr Plus divided by the glucose level measured by the Toshiba 200-FR analyzer. The dotted line indicates a reference line, i.e., a ratio of 1. No significant correlation was noted between the hematocrit and the ratio calculated.

TABLE 2. INTERFERENCE BY ASCORBIC ACID, URIC ACID, MALTOSE, AND ACETAMINOPHEN

Interferent concentration (mg/dL) ^a	Glucose concentration (mg/dL) ^b	Difference ^c	
		mg/dL	%
Ascorbic acid			
3.5	80.6	+0.4	+0.5
3.5	134.6	+13.6	+10.1
6	71.4	+3.6	+5.0
6	118.2	+1.6	+1.4
Uric acid			
7	80.6	-5.0	-6.2
7	134.6	+7.2	+5.3
25	80.6	-1.0	-1.2
25	134.6	+8.2	+6.1
Maltose			
10	80.6	-8.0	-9.9
10	134.6	-1.4	-1.0
200	71.4	+1.4	+2.0
200	118.2	-5.8	-4.9
Acetaminophen			
3	80.6	-1.8	-2.2
3	134.6	-4.0	-3.0
8	71.4	+1.6	+2.2
8	118.2	+0.2	+0.2

^aThe concentrations of each interferent material added.

^bGlucose concentration of sample to which each interferent material was mixed.

^cThe difference of glucose concentration measured after addition of interferent substances. This was calculated by subtracting the measured value after the addition from the value before the manipulation. Data are absolute glucose levels and the relative percentage compared to initial values. A negative value means that addition of interferent substances lowered the measured values.

($P=0.03$) but not at the middle ($P=0.066$) or high concentrations ($P=0.599$). One user generated slightly lower values compared to those from others with a small difference (up to 7.7 mg/dL).

Effect of PaO₂

Figure 5 shows the results of arterial blood samples with PaO₂ values ranging from 51.6 to 189.4 mm Hg. Measured

glucose values in arterial whole blood and plasma were not affected by PaO₂ ($R^2=0.0302$, $P=0.086$).

Discussion

Most patients with diabetes depend on a glucometer for their blood glucose control. Glucometer readings are used to guide patients to adjust insulin dosages in type 1 diabetes, and many type 2 diabetes patients are also using a glucometer to monitor their blood glucose levels.¹² Thus, the analytical performance of the glucometer is of considerable importance as severe inaccuracies, imprecisions, or interferences may lead to inadequate treatment and adverse reactions. There is no guideline that specifies the quality goals only for precision. Most guidelines recommend total analytical goals, such as 5% from the American Diabetes Association¹³ or 10% from the Clinical Laboratory Improvement Amendment 88 goal. None of currently used glucometers meet the above criteria. In this study, GlucoDr Plus was found to have a precision that was similar to or better than that of the other commercially available glucometers tested. Precision using patient samples was also excellent, although the CV was a little higher at low concentrations, which was expected. The International Standard Organization also recognizes this and thus recommends that the imprecision results should be reported in terms of CVs at glucose concentrations >75 mg/dL and that SDs should be reported at concentrations <75 mg/dL.¹¹ In terms of linearity, GlucoDr Plus showed excellent linearity in the range of 32.5–786.5 mg/dL. The majority of commonly used glucometers do not guarantee linearity at >500 or 600 mg/dL or <40 mg/dL.^{4,14} This wider linear range of GlucoDr Plus may give some additional use for patients with extremely low or high levels of glucose that require immediate medical attention. The instrument may also be useful for neonates, who frequently have exceptionally low glucose levels,¹⁵ and for those patients suffering from brittle diabetes with uncontrollable glucose levels. However, further validation with samples from patients with various clinical conditions, such as dehydration, hemoconcentration, acidosis, or hypoglycemia, is required. In terms of correlations with automated chemistry analyzer findings, the results of all glucometers were comparable.

Because the red blood cell has less water than plasma, the amount of water may change in whole blood depending on

TABLE 3. CORRELATIONS OF GLUCODR PLUS AND SIX OTHER GLUCOMETERS WITH THE TOSHIBA 200-FR AUTOMATED CHEMISTRY ANALYZER

Glucometer	Range (mg/dL) ^a	Slope (95% CI) ^b	Intercept (95% CI) ^b	Mean bias (mg/dL) ^c	Correlation coefficient ^d
GlucoDr Plus	29–309	0.963 (0.942–0.983)	-5.772 (-7.845 to -3.700)	-9.1 (-10.2 to -8.1)	0.993
Accu-Chek	28–312	0.924 (0.910–0.938)	-3.447 (-4.895 to -2.000)	-10.2 (-11.2 to -9.3)	0.996
OneTouch Ultra	30–309	0.965 (0.936–0.994)	-5.660 (-8.618 to -2.703)	-8.8 (-10.3 to -7.3)	0.987
Optium Xceed	20–321	1.042 (1.019–1.066)	-13.735 (-16.172 to -11.299)	-9.9 (-11.2 to -8.7)	0.992
Mi-rae 3.3G	17–330	0.998 (0.965–1.031)	-17.649 (-21.038 to -14.260)	-17.8 (-19.5 to -16.2)	0.984
Gluchec	30–320	0.867 (0.836–0.897)	9.198 (6.085–12.312)	-2.7 (-4.7 to -0.8)	0.964
MWD Pen Sensor	24–235	0.988 (0.964–1.013)	-1.220 (-2.978–0.538)	-2.0 (-2.8 to -1.2)	0.991

^aRange of glucose levels measured using each glucometer.

^bSlope and intercept of regression analysis between each glucometer and the Toshiba 200-FR. Ninety-five percent confidence intervals of each value are given in parentheses.

^cDifference between the glucose levels on the glucometer and the Toshiba 200-FR. A negative value means that the glucometer generated lower values of glucose compared to those resulting from the Toshiba 200-FR. Ninety-five percent confidence intervals of each value are presented in parentheses.

^dPearson's correlation coefficient between the glucose levels on the glucometer and the Toshiba 200-FR.

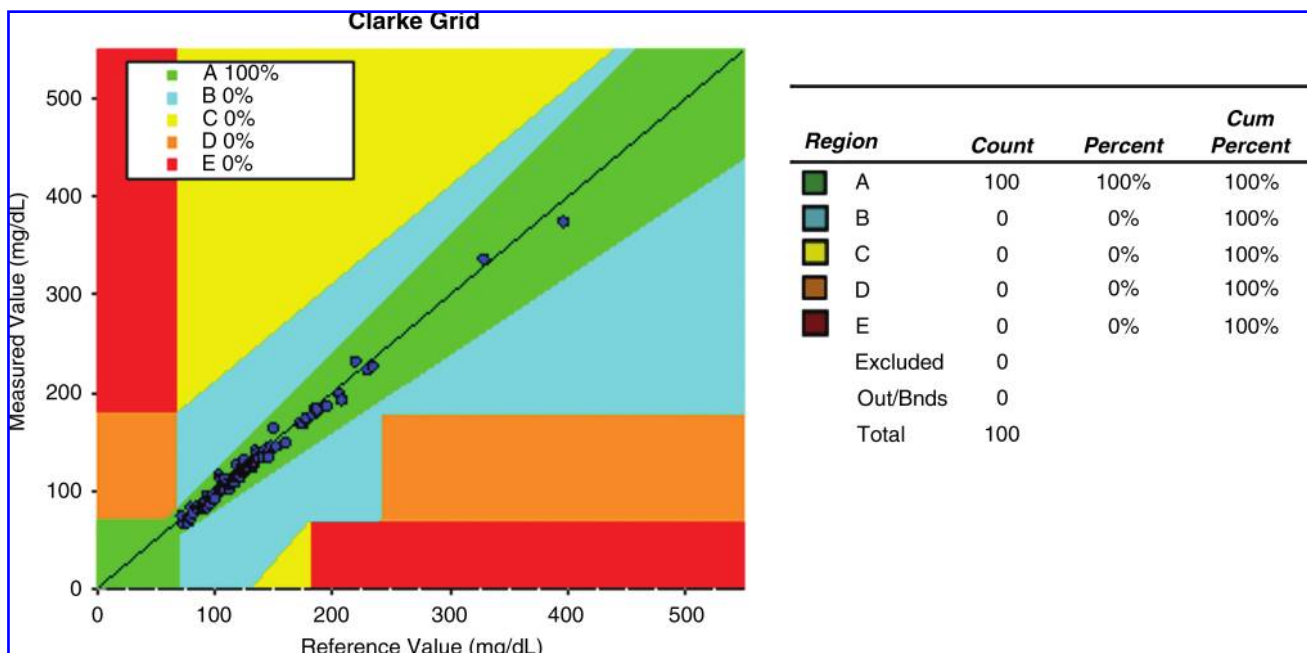


FIG. 3. Clarke error grid analysis of GlucoDr Plus measurements. The x-axis displays the glucose level recorded by the Toshiba 200-FR analyzer, and the glucose level generated from the GlucoDr Plus is displayed on the y-axis. All the measured values are in zone A, i.e., acceptable error range.

the hematocrit. Therefore, it is known that blood glucose is measured lower than its true concentration because the amount of water becomes similar to that of plasma as the hematocrit gets higher.¹⁶ Compared to the automated chemistry analyzer, GlucoDr Plus appeared to produce slightly lower values as hematocrit levels increased, although this was not significant. The interference caused by various substances is one of the mostly easily overlooked problems associated with glucometer use. Ascorbic acid is the most well-known interferent, and high levels of ascorbic acid may cause positive

or negative divergences.¹³ In the present study, ascorbic acid, uric acid, maltose, and acetaminophen caused less than 11% differences in glucose levels. Higher level of interferents would have probably caused more severe interference, but higher levels were considered clinically unnecessary. GlucoDr Plus uses FAD extracted from *Aspergillus oryzae* as the cofactor, and it has been shown that the FAD-glucose dehydrogenase system is insensitive to oxygen and has high substrate specificity.¹⁷ Furthermore, PaO₂ had no significant effects on

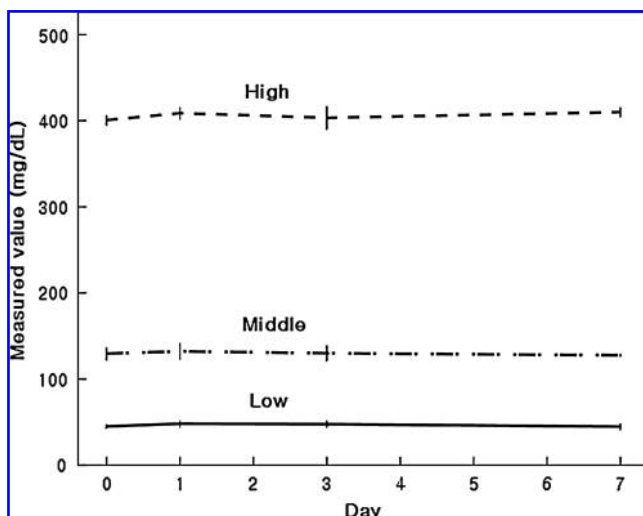


FIG. 4. Strip stability of GlucoDr Plus measurements. The day after opening is given on the x-axis. Measured values are glucose levels measured by the GlucoDr Plus expressed as means \pm 2 SEs.

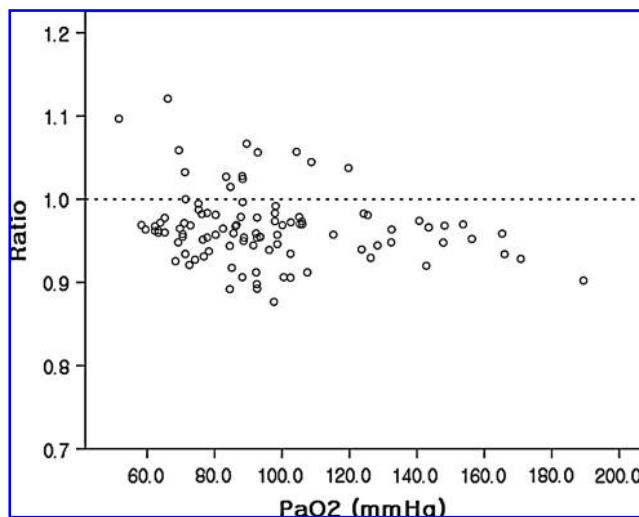


FIG. 5. Effect of PaO₂. The ratio was calculated as the glucose level measured by the GlucoDr Plus divided by the glucose level measured by the Toshiba 200-FR analyzer. The dotted line indicates a reference line, i.e., a ratio of 1. No significant correlation was noted between the PaO₂ and the ratio calculated.

GlucoDr Plus, and test strip stability was maintained for a week. The effects of longer test strip exposure periods and other environmental factors, such as temperature and humidity, should be determined by further study.

We evaluated the performance of GlucoDr Plus, a new FAD-glucose dehydrogenase-based electrochemical glucometer, using a standardized protocol. GlucoDr Plus matched or bettered the performances of other commonly used devices. We suggest that GlucoDr Plus is suitable for the self-monitoring of blood glucose in patients with diabetes.

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Author Disclosure Statement

No competing financial interests exist.

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