Original Article

Self-monitoring of Blood Glucose can be Misleading without Periodic Re-calibration of Glucose Meters: A Pilot Study

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Abstract

Introduction/Background: Diabetes mellitus is highly prevalent in both developed and developing countries today affecting about 429 million adults globally and is expected to rise by 147% to 629 million in 2045. Effective management of diabetes mellitus requires the periodic measurement of fasting plasma glucose. Self-monitoring blood glucose has been used to achieve this for over three decades now. This study, therefore, assesses the performance of three blood glucose meters used by patients with diabetes in our environment. **Materials and Methods:** This study adopted a comparative analytical prospective design that involved three of the frequently used glucose meters in our environment namely RUBY®, ONCALL®, and FINETEST®. Glucose calibrators of increasing concentrations from 40 mg/dL to 200 mg/dL were prepared from a freshly constituted 1800 mg/dl stock solution of glucose. Sera obtained from five patients were assayed along with control sera using a routine laboratory method (glucose oxidase [GOX]) for standardization and the three glucose meters simultaneously and the results were compared for statistical differences on Microsoft Excel using means and standard deviation. $P \leq 0.05$ was set as a level of significance. **Results:** The mean glucose values of calibrators (120 ± 63.3) were statistically significantly different from the mean glucose values of the RUBY (139.6 ± 80.9), ($P = 0.0118$) and the ONCALL (188.8 ± 82.1), ($P \leq 0.0001$) glucose meters, respectively. The percentage increase in blood glucose estimation by the RUBY and ONCALL devices was 115.8% and 157.3% respectively. The FINETEST glucose meter overestimated glucose by 232.0% higher than the laboratory GOX method even though there was no statistical significance ($P = 0.062$) between the two means. The percentage imprecision for the different glucose meters was: RUBY 9.5%, FINETEST 14.8%, and ONCALL 18.2%. **Conclusion:** Quality control should be used routinely in the use of point of care testing glucose measurements and devices should be sent to the central laboratory periodically for recalibration to avoid mismanagement of diabetic patients on hypoglycaemic drugs.

Keywords: Diabetes mellitus, point of care testing, self-monitoring of blood glucose

Introduction

Diabetes mellitus is a non-communicable disease with a high prevalence today affecting about 429 million adults globally and is expected to rise by 147% to 629 million in 2045.[1] According to the American Diabetes Association, diabetes can be diagnosed using plasma glucose concentrations above acceptable cut-offs in the presence of symptoms suggestive of hyperglycemia. Fasting plasma glucose ≥7.0 mmol/L (126 mg/dl) and 2 h plasma glucose level ≥11.1 mmol/L (200 mg/dL) following a 75 g glucose drink dissolved in 250 mL to 300 mL of water are considered to be in the diabetic range.[2] Duration of fasting is expected to last for at least 8–10 h overnight and the test is conducted at dawn.

Diabetes mellitus can also be diagnosed using glycated hemoglobin (HBA1c). HBA1c is formed when glucose combines nonenzymatically with the N-terminal valine residue of each beta chain of hemoglobin A. The formation of HbA1c is irreversible and the blood concentration relies on both the half-life of the erythrocytes and the level of blood glucose. HbA1c has been approved for the diagnosis of both prediabetes (≥5.7%) and diabetes (≥6.5%).[3]

Effective management of diabetes mellitus requires the periodic measurement of both fasting plasma glucose and HbA1c. The practice of using self-monitoring blood glucose (SMBG)

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alongside glucose meters has been around for over three decades now.[4] It allows patients to perform glucose testing by themselves or their relatives and Keep records of their blood glucose readings. The aim is to achieve early blood glucose control which has numerous benefits such as delay in onset of hyperglycemic complications[5] and reduction in the frequency of hospital visits. SMBG also allow patients to get involved in the management of their condition and allow the incidence of hypoglycemia while attempting to achieve tight glycemic control. To achieve these benefits, the results obtained from glucose meters should be representative of the true glycemic states of the patients. However, this may not always be true due to some factors. One such factor is the stability and reliability of the blood glucose measuring instrument used. Point of care testing (POCT) devices can malfunction leading to falsely high or low results with the consequence of mismanagement of the patient's condition.[6] This study, therefore, compared the performances of three blood glucose meters used by diabetes patients with the routine glucose oxidase (GOX) method used in our laboratory.

Materials and Methods

Study site

The study was carried out in the Department of Chemical Pathology of the University of Calabar Teaching Hospital (UCTH), Calabar. UCTH is a tertiary hospital located in the South-South geopolitical zone of Nigeria with over 600-bed spaces in various clinical departments staffed with specialists. It serves as a referral center to other primary and secondary health facilities in Cross River State and neighboring Akwa Ibom State.

Study design

It was a comparative analytical study that involved the calibration of different glucose meters to verify their accuracy, linearity, and reproducibility of results. We used three of the frequently used glucose meters by patients in our environment namely Medismart® RUBY blood glucose monitoring system-Lobeck Medical AG, (Schulstrasse 19 CH-5070 Frick/Switzerland), ONCALL® by ACON Diabetes Care, Califonia-USA, and Finetest® by Infopia Co. Ltd., Kyunggi, 431-080, Korea. Five different calibrators of glucose with increasing concentrations from 40 mg/dL to 200 mg/dL were prepared from a freshly constituted 180 mg/dl glucose stock solution. Two of the devices (RUBY® and ONCALL®) were used to measure the predetermined concentrations of the calibrators. A spectrophotometer (Spectro SC by Labomed Inc. Los Angeles, CA 90034 U.S.A.) in routine use in the laboratory was used to determine the absorbance of the different concentrations, and a graph of absorbance against concentration was used to determine the concentration of the control serum. The obtained value of the control serum was compared with expected. The mean and standard deviation (SD) of the concentrations of the different calibrators from the glucose meters were then calculated and compared with the concentrations of the calibrators. Different plasma samples sent to the laboratory for routine analyses were tested using the third glucose meter (FINETEST®). The results obtained were compared with the routine laboratory GOX method. A control serum was used to determine the coefficient of variation (CV) of each glucose meter. The sample was assayed using 10 glucometer strips on the three glucose meters. The mean and SDs were determined. The CV was calculated from the formula, CV = SD/mean × 100% and the results were expressed as a percentage.

Statistical analysis

Results obtained were analyzed using Microsoft Excel and Graphpad software. The mean of the different results was compared for significance using Paired-samples *t*-test at the alpha level of $P \leq 0.05$.

Results

A summary of some of the characteristics of the three glucose meters used in this study is shown in Table 1. The most a method used is the enzyme method including GOX and glucose-1-dehydrogenase (GDH). Table 2 is a representation of results obtained from two of the three glucose meters namely: RUBY and ONCALL. Statistically significant differences were observed between the mean values of glucose calibrator measurements of RUBY ($P = 0.0118$) and ONCALL ($P < 0.0001$) glucose meters. The percentage increase in glucose calibrators' estimation by the RUBY and ONCALL was 115.8% and 157.3% respectively. Figure 1 is a graphical representation of the different glucose readings by the glucose meters (RUBY and ONCALL) in relation to the calibrators. Both glucose monitoring devices appear to deviate more with increasing glucose concentration.

Table 3 is a comparison of glucose measurements from the FINETEST® glucose meter with our routine laboratory GOX method. The FINETEST glucose meter overestimated glucose

Table 1: Summary of point of care glucose meters used in the study

Company and Device	Method		Analytical Range (mg/dl)
	Enzyme	Analysis	
MediSmart® RUBY, Switzerland	FAD –GDH	Amperometric technique	20-630
ACON ON-CALL® Plus II, California, USA	GOX	Amperometric technique	20-600
INFOPIA Finetest® Auto Coding, Kyunggi, Korea	-	Amperometric technique	10-600

FAD-GDH Flavin adenine dinucleotide-glucose dehydrogenase; GOX-Glucose oxidase

Table 2- Comparison of calibrator measurements of RUBY® and ONCALL® Glucose meters using paired student's *t*-test

Variable/Test	T1	T2	T3	T4	T5	Mean±SD	Difference (%)	*P*
STANDARD (mg/dL)	40	80	120	160	200	120±63.25	-	-
RUBY® READINGS (mg/dl)	30	91	124	195	258	139.60±89.3	19.6 (115.8)	0.0118*
ONCALL READINGS (mg/dL)	62	159	207	252	264	188.80±82.1	68.8 (157.3)	<0.0001*

*P<0.05 is considered significant

Table 3: Comparison of FINETEST® glucose meter with Laboratory methods

Plasma samples	Laboratory Method (mmol/L)	FINETEST® (mmol/L)	*P*
1	4.3	9.4	
2	4.9	9.2	
3	3.8	6.7	
4	10.7	32.4	
5	5.1	11.2	
6 (control)	3.7	6.2	
Mean±SD	5.4±2.6	12.5±9.9	0.062

The reference for the control solution was 3.2-5.1mmol/L. $P \leq 0.05$ was considered significant.

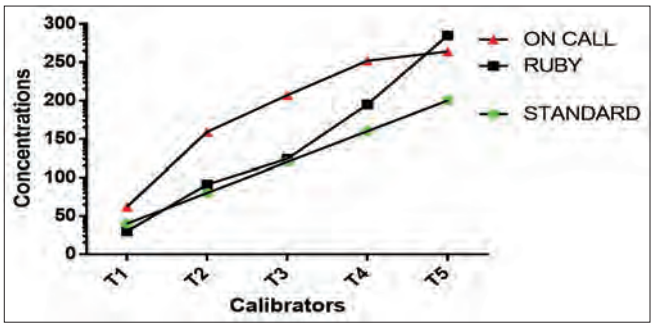

Figure 1: Graph showing the comparison of concentration of the calibrators and the results of the different glucose meters tested. T1–T5 are the different calibrators used in the experiment with the following concentrations: T1 = 40 mg/dl, T2 = 80 mg/dl, T2 = 120 mg/dl, T4 = 160 mg/dl and T5 = 200 mg/dl

by 232.0% higher than the routine laboratory GOX method although the difference between the two means was not statistically significant (P = 0.062). The reference interval for the control solution was 3.2–5.1 mmol/L. The calculated CV for the respective glucose meters was 9.5% for RUBY, 15.8% for FINETEST, and 18.2% for ONCALL.

Discussion

This pilot study has shown that results from some POCT devices used for SMBG can be significantly different from the true value and if applied to patient management may result in adverse consequences. Faulty glucose meters can either overestimate or underestimate blood glucose depending on the sources of error. Errors can come from poor storage of the device, suboptimal battery life, malfunctioning sensor, or improper storage of test strips such as exposure to atmospheric air for longer than necessary, and many more.[7] Some glucose meters also require the replacement of codes for each new batch of test strips and when this is not followed can result in unreliable results. The RUBY® glucose meter in this study on average overestimated the calibrators by up to 116.3% of the expected value while the ONCALL®overestimated the expected value by 157.3%. This is a course for worry. Putting it in perspective, the implication is that a patient with a fasting plasma glucose value of 90 mg/dl (5.0 mmol/L) by routine laboratory method will have a reading of 104.7 mg/dl (5.8 mmol/l) and 141.6 mg/dl (7.8 mmol/l) from the RUBY® and ONCALL® glucose meters, respectively. Since the aim of testing is to monitor glycemic control, it can be said that applying such results in patient management will have adverse consequences in the long run. The effect of such false results was brought to the limelight in the case of a 45-year-old man on warfarin therapy, digitalis, and beta-blockers for tricuspid valve replacement. He developed thrombosis as a complication despite 12 consecutive normal international normalized ratios results from his POCT device. A comparison with laboratory-generated results revealed that he was getting inadequate anticoagulation therapy leading to thrombosis. His therapy was adjusted in line with the new laboratory-generated results.[6] This example emphasizes the need for periodic re-calibration of POCT devices.

There are minimum required standards that must be met by POCT glucose meters as set out by International Organization for Standardization 15179: 2003.[8] These guidelines require that 95% of each glucose level are in the range of ± 15 mg/dl ≤75 mg/dl, ±20% >75 mg/dl when compared to the reference measurements.[8] Ten years later in 2013, these requirements were revised.[9] The new requirements are that at blood glucose <75 mg/dl, 99% of values should be ± 15 mg/dl; while at >75 mg/dl glucose concentration, 99% of measurements should be ± 15% of reference measurements.[9] According to the National Committee for Clinical Laboratory Standards the allowable analytical error should be <5% and total error (bias and imprecision including manipulation) should be <7.9%.[10] None of the glucose meters used in this study met these requirements. Meeting these targets of accuracy by POCT devices is a crucial factor to guide monitoring and adjustment of therapy. However, upholding test precision and performance are the major challenges in POCT. These challenges are compounded by the increasing number of different operators and instrument brands available.[7,11] To address the issue of test performance, three factors were identified as critical. According to a recent publication by the American Association

of Clinical Chemistry (AACC) Academy, the user must understand (i) the operation of the POCT device, (ii) how to troubleshoot system errors, (iii) the essence of using quality control (QC) materials (iv) how to handle and store of QC materials.[12] These are lacking in our health care setting as was observed in a previous survey carried out in our hospital.[13]

The principles used by the glucose-monitoring POCT devices can also be a source of error. Most devices employ the use of enzymes, commonly GOX and GDH as was the case with ONCALL and RUBY glucose meters used in this study, respectively. In the GOX method, the enzyme catalyzes the oxidation of glucose to gluconic acid and hydrogen peroxide. This first step is very specific to glucose and the observed level of hydrogen peroxide is related to the level of glucose in the sample. The difference in the concentration of hydrogen peroxide is monitored photometrically with a chromogen that will produce a color change or amperometrically by measuring the amount of electric current generated. The second step which involves a peroxidase is not as precise as the reaction of GOX. This is because elements such as uric acid, ascorbic acid, bilirubin, tetracycline, and glutathione inhibit the reaction with attendant drop in glucose level.[14]

The GDH enzyme catalyzes the oxidation of glucose to gluconolactone. In older glucose measuring instruments, a coenzyme is used to reduce nicotinamide adenine dinucleotide (NAD) to NADH. The level of NADH can be measured photometrically or amperometrically – as used in all devices in this study and is proportional to the blood glucose concentration. Newer devices make use of the coenzyme pyrrolo-quinolinequinone (PQQ) which is less sensitive to ambient oxygen and electrochemical interference. Although the method produces results in close agreement with the reference hexokinase method, products containing maltose or galactose spuriously increase results obtained with POCT that use GDH-PQQ. Both methods have been adapted on autoanalyzers for use in central chemistry laboratories with various modifications to reduce interference and improve the accuracy of results.[14,15] Results from this study will go to suggest that the GDH method is more accurate than the GOX method since the RUBY meter has the smallest percentage imprecision.

Operator education and training are key factors that have been identified to improve test performance.[16,17] These have a direct bearing on user competency. Most operators of POCT devices in our hospitals learned how to operate the device from friends, health care workers, instrument vendors or product leaflet among others.[13] Granted, the operation of POCT glucose meters are classified as waived testing under the CLIA '88 and as such require minimal training to operate,[18] and newer models are designed with technological advances that decrease operator errors,[19] however, there are evidence that user competency can affect the quality of results. A study by Huang *et al*.[20] assessed the effect of user proficiency on the rational operation of glucose meters. The number of QCs performed by each operator was used as an indication of competency and the degree of inaccuracy of the measurements indicating the level of analytical performance. After analyzing up to 59,000 QC points from 20 different glucose meters, they found that users who performed fewer QC tests were more likely to generate results with greater imprecision.[20]

Although understanding the use of QC materials was identified as a crucial factor in the assessment of the analytical performance of POCT devices,[12] this practice is not common among our POCT device operators, neither in the hospital setting[13] nor among diabetics who practice SMBG. In one recent survey, only about a quarter of respondents admitted to using QC materials on their POCT devices.[13] One possible reason for this low practice may be due to a lack of knowledge of the benefits associated with the use of control materials routinely. This can be addressed by the education of POCT operators and the availability of POCT QC materials by the central laboratory. As shown by Huang *et al*.,[20] periodic QC can be used to access the percentage imprecision of an instrument over a long period. All these will be possible if each hospital sets up a QC Monitoring Committee as recommended by the AACC Academy.[12]

There are some limitations to this study. It was not feasible for us to estimate the percentage imprecision of the glucose meters over a long period due to the lack of regular QC practices by the operators. Another limitation was the low number of calibrators tested. Testing at least 20 calibrators and sera by the glucose meters and laboratory methods would have strengthened our conclusions reached. However, despite these limitations, this pilot study has highlighted the importance of periodic calibration of glucose meters and the potential benefit of regular use of QC materials while testing.

Conclusion

There is a need to introduce QC into POCT in our hospitals. This can be facilitated by encouraging management to constitute a POCT committee and educating operators of such devices to submit the same for routine quality checks. The different QC values from the various POCT devices can be periodically analyzed to ascertain their performances. This will improve the quality of results generated from point of care glucose meters and the overall management of diabetes patients using SMBG in our environment.

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Conflicts of interest

There are no conflicts of interest.

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