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COMMENTARY

Glucose Information for Tight Glycemic Control: Different Methods with Different Challenges

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Abstract

Rigorous glucose control is essential for prevention of diabetes-related complications in diabetes patients. Even without diabetes, tight glucose control is beneficial in hospitalized, critically ill patients.

Actually, three different glucose measurement methods are used: (1) hand held devices, (2) blood-gas analyzers, and (3) laboratory analyzers in core laboratories. Each method is subject to specific challenges and limitations that can affect the overall system performance.

In this article, we aim to demonstrate that even glucose measurement results from core laboratories (professional laboratory systems) do not necessarily reflect the absolute "true" glucose level of a patient.

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Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia or hypoglycemia, resulting from defects in insulin secretion, insulin action, or both.

Since the publication of the seminal studies of the Diabetes Control and Complications Trial (DCCT; for type 1 diabetes) and the United Kingdom Prospective Diabetes Study (UKPDS; for type 2 diabetes), there is consensus that tight glycemic control represents a cornerstone in the prevention of diabetes-related complications in outpatient care.

Hospitalized patients (with and without diabetes as an underlying condition) and especially those treated in intensive care units (ICUs) are even more prone to dysregulations of the glucose metabolism, with a considerable consequent risk for higher mortality rates.

Measurement of glycemia in plasma or blood is therefore inalienable in the management of diabetes mellitus or otherwise altered glucose metabolism.

Three different methods are available for the measurement of glucose levels: (1) small handheld devices

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Abbreviations: (A1C) glycosylated hemoglobin A1c, (BG) blood glucose, (BGA) blood-gas analyzer, (DCCT) Diabetes Control and Complications Trial, (FAD) flavine adenine dinucleotide, (GDH) glucose dehydrogenase, (GOx) glucose oxidase, (ICU) intensive care unit, (IFCC) International Federation of Clinical Chemistry and Laboratory Medicine, (ISO) International Organization for Standardization, (NAD) nicotinamide adenine dinucleotide, (NADPH) reduced nicotinamide adenine dinucleotide phosphate, (PQQ) pyrrolo quinoline quinine, (SMBG) self-monitoring of blood glucose, (UKPDS) United Kingdom Prospective Diabetes Study

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[self-monitoring of blood glucose (SMBG)] for the measurement of capillary blood samples, principally designed for self-measurement of glucose values by the patient itself but sometimes also used in hospital wards ("bedside testing"); (2) more sophisticated devices, usually able to determine a couple more laboratory values (e.g., blood-gas analysis and electrolytes) and principally designed for use in intensive or intermediate care units [i.e., blood-gas analyzer (BGA)], in Europe often referred to as "point-of-care testing;" and (3) central laboratories that are spatially separated from the care units.

The aim of this article is to highlight the accuracy, differences, and limitations of these three methods and the implications for therapy.

Chemistry Principles

Three different methods are predominantly used to determine glucose concentrations:

1. Glucose oxidase (GOx) method: The enzyme GOx catalyzes the oxidation of glucose into gluconolacton and H_2O_2 (hydrogen peroxide). In a subsequent peroxidase-mediated indicator reaction, H_2O_2 oxides a reduced chromogen (a leuco dye) under development of color, which can be measured by photometry. The color intensity is proportional to the glucose concentration.

2. Hexokinase method: Glucose is phosphorylated in the presence of hexokinase and adenosine triphosphate to glucose-6-phosphate. This compound reacts with nicotinamide adenine dinucleotide (NAD) phosphate, creating 6-phosphogluconate and reduced nicotinamide adenine dinucleotide phosphate (NADPH), catalyzed by glucose-6-phosphate-dehydrogenase. The rise of NADPH until the end of the reaction is measured, and the rising optical extinction is proportional to the glucose concentration in the sample.

3. Glucose dehydrogenase (GDH) method: Glucose is oxidized by GDH to gluconolacton. The released hydrogen is transferred to NAD, creating NADPH. The rise of the latter until the end of the reaction is measured, the rising extinction being proportional to the glucose concentration in the sample.

SMBG systems employ very diverse biochemical reactions. Coenzymes flavine adenine dinucleotide (FAD), pyrrolo quinoline quinine (PQQ), and NAD can be found. Glucose oxidases or dehydrogenases catalyze the oxidation of glucose, but nearly every product is unique with respect to many important features. Simple rules such as "PQQ is bad for specificity and FAD is good" are misleading. Specificity is determined by the enzyme protein and not by the coenzyme. A review of these methods and of their advantages and disadvantages is far beyond the scope of this article.

The general chemistry principles are essentially the same in BGA devices and in central laboratory analyzers, with the main difference that a "wet chemistry principle" and different detection methods (e.g., direct electrodes) are used. This has an implication for the samples used for analysis. The SMBG devices are only designed for testing capillary blood samples; most of these devices provide a plasma equivalent value (as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine [IFCC]). Even when labeled correctly, this may lead to confusion or possible errors. The "wet chemistry" procedure allows an analysis of whole blood, hemolyzed whole blood, or plasma from venous, arterial, or capillary sources.

The identification and documentation of the type of the sample is crucial in this case, because fasting glucose values in venous blood are 5–10% lower than in arterial samples, as capillary samples are showing 5–15% higher values compared to venous blood samples. Similarly, venous or capillary plasma samples are showing 10–15% higher values compared to whole blood hemolysate; deproteinization of samples have a similar effect due to the "volume displacement effect."[1]

Regulatory Standards

SMBG systems are medical devices and belong to the group of *in vitro* diagnostics. In Europe, SMBG systems have to comply with the directive 98/79/EC on *in vitro* diagnostic medical devices, which specifies general requirements to ensure overall safety and quality.[2] The standard DIN EN ISO 15197:2003 specifies requirements for SMBG systems, e.g., with regard to system performance, accuracy, and precision.[3] The minimum acceptable system accuracy requirements are based on the medical requirements for glucose monitoring: "≥95% of the individual glucose results shall fall within ±15 mg/dl of the results of the manufacturer's measurement procedure at glucose concentrations <75 mg/dl and within ±20% at glucose concentrations ≥75 mg/dl."[3] Manufacturers of SMBG devices have to provide evidence of conformity with the standard DIN EN ISO 15197:2003 in order to get the Conformité Européenne label for their products.

Stricter accuracy requirements for SMBG systems are under consideration for implementation by both the Food and Drug Administration and the International Organization for Standardization (ISO).[4–7] Obviously, even a smaller number of SMBG systems currently on the market will fulfill these stricter requirements.[8]

The standards for BGAs and central laboratory systems follow—beyond ISO norms—mainly recommendations of the IFCC, the Clinical and Laboratory Standards Institute, and the College of American Pathologists (with a special focus on the United States). Accuracy and precision are assured by comparing measurements internally (e.g., lot-to-lot variation and between-cartridge variation) and externally (between-device variation by comparing standard test samples in different laboratories, so-called "proficiency testing"). Results of these quality tests often serve as reference value in the assessment of the accuracy and precision of SMBG devices.

Confounding Factors

A number of possible confounding factors, independent from the methodology used, may have to be taken into consideration before translating the measurement results into clinical action.

Limitations of the systems include substance interferences and performance parameters. Substance interferences refers to interference of the system with any substance present in the blood at increased or abnormal concentration that affects the reliability of the blood glucose (BG) results. Substances interfering with the determination method can either originate from drugs taken by the patient or from therapies initiated by the medical staff or are naturally occurring in the blood. Examples are acetaminophen, ascorbic acid, dopamine, icodextrin, bilirubin, triglycerides, and paraproteins.[9]

Performance parameters refers to limitations due to the specifications and technology of a system, e.g., hematocrit values may play a very important role in blood samples taken in an inpatient context. Hematocrit values of 25% may result in artificially high glucose results by 25% and inversely for values above 65%. **Table 1** shows the role of important performance parameters, again of different SMBG systems.

But as there are only three general chemistry principles underlying the three measurement methodologies, it is important to point out that confounding factors are, in principle, germane to any of them, whereas the hexokinase method is the least prone to analytical interactions.[10]

Table 1.
Performance Parameters of Different Self-Monitoring Of Blood Glucose Systems[a]

Parameter[b]	Accu-Chek® Aviva	Accu-Chek® Compact Plus	OneTouch Ultra2®	Ascensia Contour® II	FreeStyle Lite®/ FreeStyle Freedom®	Precision Xtra®
BG measurement range (mmol/liter)	0.6–33.3	0.6–33.3	1.1–33.3	0.6–33.3	1.1–27.8	1.1–27.8
Hematocrit (%)	20–70	25–65	30–55	0–70	15–65	30–60
Humidity (%)	10–90	20–85	10–90	10–93	5–90	10–90
BG test strip stability	EXP on BG test strip vial (date of manufacture + 18 months)	EXP on BG test strip vial (date of manufacture + 18 months) or PAO 3 months	PAO 3 months	EXP on BG test strip vial or PAO 6 months	EXP on BG test strip vial	EXP on BG test strip vial
Operating temperature (°C)	+6 to +44	+10 to +40	+6 to +44	+5 to +45[c]	+5 to +40	+10 to +50
Underdose protection	yes	yes	no	yes	yes	yes
Double dosing	yes	yes	no	yes	yes	yes
Altitude (m)	<3094	<4000	<3000	<3000	<3000	<2200
Total cholesterol (mmol/liter)	<13.0	n/a	<18.1	<13.0	<13.0	<13.0
Triglycerides (mmol/liter)	<54.7	<57.0	<34.2	<34.2	<34.2	<11.4

[a] EXP, expiry date; PAO, period after opening
[b] Taken from product user labeling of the SMBG systems.
[c] When moving the BG meter Ascensia Contour from one location to another with a different temperature, Bayer recommends to allow 20 minutes for temperature adjustment; temperature variations are given in the BG test strip package.

Additional potential interferences should be considered. Blood-gas analyzer and central laboratory results are more prone to pre-analytical errors, e.g., the choice of wrong test tubes, erroneous or missing labeling of vials, partial filling of vials, or long time gaps between collection and analysis of the samples, leading to a degeneration of glucose.

Operator influence is probably more pronounced in the SMBG method, as it is often used by laypeople.

Table 2 provides a qualitative overview on confounding factors and potential interferences for the three methods.

Accuracy and Precision

Generally, accuracy is defined as the closeness of agreement between a test result and the accepted reference value and precision is defined as the closeness of agreement between independent test results obtained under stipulated conditions.[2]

In the case of the analysis of BG, the situation is complex because (A) BG is an unstable analyte, i.e., BG is degraded gradually by glycolysis after blood sampling, and (B) there is no whole BG standard available, which is usually a prerequisite for establishing accuracy of measuring devices.[7]

The correct meaning of these so-called specific performance characteristics is not always clear in the laboratory medicine area, both on the side of laboratory users and manufacturers.[11] Moreover, the use of terms describing specific performance characteristics, such as "accuracy," "precision," "trueness," and "total error," differs partially between locales, e.g., the United States and Europe. This shall be kept in mind if analyzing the respective literature published so far. We would recommend to adhere to the definitions given in ISO 3534-1:1993,[12] ISO 5725-1:1994,[13] and ISO 15197:2003.[2]

There is a plethora of literature commenting on the performance of portable glucose meters compared to laboratory values, and it would be beyond the scope of this article to review them in detail. In this context, we would like to point to a study by Boyd and Bruns,[14] where a simulation of insulin dosing errors due to BG measurement errors was performed.

Table 2.
Influences on System Performance and Consequent Risk of Error[a]

Influence	Handheld devices		BGAs		Core Laboratory	
	Factor	Risk of error	Factor	Risk of error	Factor	Risk of error
System accuracy	+ / ++	+ / ++	++	+	++ / +++	+
Operator influence	PwD /layperson HCP	+++ +	HCP	++[1]	HCP	+[b]
Blood sample type	capillary	None to low	Arterial, venous, mixed, or capillary (whole blood)	Low[c]	Arterial, venous, mixed, or capillary (varying sample presentations)	Potentially high[d]
Blood sample transfer	None	n/a	Short	Low	Long	Potentially high[e]
Blood sample stabilization	None	n/a	None[c]	Low	e.g., EDTA, heparin, NaF	Low to medium[f]
Blood sample storage	None	None	Short-term	Low	Long-term	Low to medium[e]
Environmental conditions	Varying environmental conditions	Medium to high	Mostly controlled conditions	Low	Controlled laboratory conditions	Very low
Blood sample matrix	Whole blood	Whole blood	Whole blood	Low	Blood plasma	Low

[a] Dilution effects if sample taken from arterial or central venous lines. PwD, person with diabetes; HCP, health care professional; EDTA, ethylenediaminetetraacetic acid
[b] Mainly automated.
[c] Sometimes preheparinezed vials used.
[d] Erroneous or missing labeling of the sample.
[e] Nonrespect of required transport conditions.
[f] Erroneous use of nonappropriate sample tubes/vials.

They concluded that portable BG meters, if they are meeting the current quality standards, permit at a high percentage the administration of insulin doses intended to reach the target glucose range. But the same study also indicated that large errors of insulin doses (≥4 U of insulin) occurred nevertheless in over 5% of the time when the coefficient of variation exceeded 10–15%.

An overview of Bergenstal[15] and a study of Koschinsky and colleagues[16] are heading in the same direction, showing that results of portable meters are, in principle, reliable and able to guide treatment options, if reasonable safety margins are added to the targeted glucose range.

Breton and Kovatchev[17] investigated the impact of SMBG errors on the short- and long-term response to insulin and glucose challenges in type 1 diabetes patients, using a sophisticated computer simulator representing the human metabolic system. Their findings underline that glucose variability, the detection and the risk of hypoglycemic events, and achievement of target BG values can be improved by tightened system accuracy requirements. Such model-based findings may be very helpful as long they imply all relevant factors occurring in the real world of a clinical setting.

At least, there seems to be consensus that different patient groups (i.e., patients with type 2 diabetes and oral antidiabetic therapy, patients with type 1 diabetes and intensified insulin therapy, and patients in the ICU) deserve different levels of accuracy.[18]

In one study, Freckmann and associates[8] evaluated 27 BG monitoring systems from 18 manufacturers for system accuracy according to DIN EN ISO 15197:2003. Twenty-four systems were compared with the GOx reaction (YSI 2300 Glucose Analyzer) and 3 systems with the hexokinase reaction (Roche Hitachi 917). Duplicate measurements of 100 blood samples with a defined distribution of BG concentrations from 20 to 600 mg/dl from ≥100 subjects were included in the evaluation. Of 27 SMBG systems, 16 fulfilled the minimum accuracy requirements of the standard ISO 15197, i.e., ≥95% of their results showed the minimum acceptable accuracy.

Astonishingly, there is a paucity of published papers dealing with the performance of BGA devices—or central laboratory results. The data available so far (i.e., from between-laboratory standard sample assessments of the College of American Pathologists[19] and its counterpart in Germany,[20] as well as other sources[21,22]) indicate a precision and accuracy of the laboratory results of ±10%, generally considered as acceptable and probably more accurate and trustful than results from SMBG devices. One has to keep in mind that these values refer to the analysis of standard samples and do not represent the (higher) total error, because it does not accommodate errors that accompany pre-analytical errors and potential interferences described earlier.

Furthermore, a clear distinction should be made between outpatient diabetes management and tight BG control in the ICU. In the latter case, patients are often in very specific conditions (e.g., jaundice, dyslipidemia, or tolerated anemia), which are usually not present in patients for which handheld devices have originally been designed, and a couple of publications point to the related problems in critically ill patients.[23,24]

Summarizing Comment

The DCCT[25] and the UKPDS[26,27] could demonstrate the paramount importance of intensified therapy to prevent diabetes related complications and that there is a good correlation between glycosylated hemoglobin A1c (A1C) levels and the respective patient-relevant end points.[28–30] Apparently, the existing level of accuracy of SMBG systems has been sufficient to achieve major improvements in the metabolic situation of patients with diabetes.

However, there is now a growing body of evidence that not only average A1C values but also short-time glycemic peaks and nadirs (in terms of minutes or hours, glycemic variability) represent an independent risk factor for diabetic complications[31–33] and that short-term peaks are not necessarily reflected by an increased A1C value.[34–37]

Postprandial and fasting glucose are without doubt the main contributors to A1C levels and intraday glycemic variability,[38–40] and over 15 studies published since 1998 demonstrated that elevated postprandial glycemic values contribute to an approximately three-fold risk to develop coronary heart disease or a cardiovascular event.[41]

On the other side the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation and the Action to Control Cardiovascular Risk in Diabetes study demonstrated that too tight glycemic control comes along with a higher risk of severe hypoglycemic events and higher mortality in outpatient care.[42,43]

In the field of inpatient care, interest in tight glycemic control was raised after the seminal study

of Van den Berghe and coworkers,[44] leading to recommended glycemic targets of 80–110 mg/dl for ICU patients. Today, the targets for glycemic control in the ICU appear to be less stringent, after the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis and Glucontrol studies[45,46] demonstrated unacceptable rates of hypoglycemia in critically ill patients receiving intensive insulin therapy. Subsequent studies (especially Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation[47]) and meta-analyses[48,49] confirmed that too tight control was associated with an increased risk of severe hypoglycemia without the benefit of significantly reduced hospital mortality.

An explanatory hypothesis could be that the care teams put too much trust in the results of the devices or methods used, considering them as absolute "true values" and ignoring that a total error is imminent to all techniques available. Blood glucose analyzers and core lab methods may have a higher analytical accuracy and precision on their own, compared to SMBG devices, but the advantage could be outweighed by the numerous possible pre-analytical errors related to the first two methods (see **Table 2**). Actually, the total error of core lab methods seems to be in the range of 8% to 10%.[19,20]

We would argue that the solution might be less in the direction of stricter standards, as a total error will remain, independent of whether SMBG, BGA, or central laboratory results are used for the implementation of a therapeutic strategy.

Practitioners, especially in the ICU, should weigh the advantages and disadvantages of the respective methods: a greater bias with potentially lower pre-analytical errors versus a somewhat lower bias but with a higher potential for pre-analytical errors.[50]

So, the introduction of more strict standards would not resolve the problem of the possible pre-analytical errors and/or other confounding factors. Instead, it seems advisable to consider a 10–15% safety margin at the limits of the targeted glycemic range to allow for the sources of error due to the circumstances of the measurement procedure, independent from the methodology used.

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