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Review

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Point-of-care testing in diabetes management

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Abstract

The prevalence of diabetes mellitus (DM) has rapidly increased over the last decades, reaching epidemic magnitudes, particularly in low- and middle-income countries. Point-of-care (POC) technology enables decision making near or at the site of patient care. Portable blood glucose meters and HbA1c testing are used by the healthcare provider and millions of patients with diabetes to monitor the safety and effectiveness of the diabetes treatment. However, POC capillary blood glucose and POC HbA1c testing are not recommended for diabetes diagnosis. Rather, they have been used for screening diabetes in low- and middle-income countries to decrease the disease burden.

Keywords*: point-of-care, advanced medicine, monitoring systems, bedside testing*

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Introduction

According to The International Diabetes Federation, 425 million adults had diabetes in 2017, and the figure is expected to reach 629 million in 2045 (1).

Diabetes is diagnosed based on plasma glucose levels (either fasting plasma glucose ≥126 mg/dL or a 2-h plasma glucose value during a 75-g oral glucose tolerance test ≥200 mg/dL) or HbA1C ≥6.5% (2).

Glycated hemoglobin (HbA1c) is a form of hemoglobin produced in a non-enzymatic glycation pathway by hemoglobin exposure to plasma glucose. It reflects average blood glucose levels over the past 3 months and has a strong predictive value for diabetes complications (3, 4). Monitoring HbA1c levels in patients with diabetes has been used as an indirect measure of average glycemia in several landmark studies of diabetes therapy (3, 4). HbA1c testing is performed routinely in all patients with diabetes, along with other tools such as blood glucose monitoring, to optimize glycemic control. More recently, HbA1c measurement has been used for diagnosing prediabetes and diabetes (5). Values ≥5.7% define prediabetes, while values ≥6.5% are characteristic of diabetes.

POC or bedside testing is known as medical diagnostic testing that provides immediate re-

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sults using transportable instruments or test kits, performed by clinical staff without laboratory training. It also includes patient self-monitoring. Today, cheaper, faster and reliable POC testing instruments offer onsite results that reduce the time spent with classic laboratory measures (6).

POC blood glucose monitoring test in diabetes management

Early detection and intervention is crucial in diabetes management. Lifestyle interventions reverse prediabetes and result in a reduction of diabetes incidence over more than ten years (7). The benefits of achieving early glycemic control in the natural history of diabetes are important: every 1% reduction in HbA1c results in a 37% reduction in microvascular complications, a 43% reduction in amputations, a 21% reduction in death from peripheral vascular disease, and a 14% reduction in myocardial infarctions (4).

Diabetes and prediabetes may be *screened and diagnosed* based on the same tests: plasma glucose levels or HbA1c levels (2). Glucose levels should be assessed in plasma separated immediately after blood collection.

Glucose testing using glucose meters became a practice in the health care system around 1987 and it has been perfected from 1.2 kg instruments to light weight pocket-size devices. POC capillary blood glucose testing is currently used by health care providers and millions of diabetic patients. However, POC blood glucose testing is not recommended for diabetes diagnosis. Rather, it has been used for screening diabetes in low- and middle-income countries to decrease the disease burden (8).

Self-monitoring blood glucose (SMBG) is intended especially for patients that use multiple insulin injections per day or insulin pumps for diabetes treatment. Patients should monitor their glycemic value before every meal or snack, from time to time in postprandial state, during the night, when symptoms of hypoglycemia appear, and after they correct it, before driving, before and during exercising. Glycemic values can be determined up to 6-10 times per day (9). The benefit of structured SMBG in the management of insulin treated patients is well-established (10). Moreover, regular SMBG use in non-insulin treated patients also has a favorable impact on glycemic control (11, 12).

It is very important for SMBG to be integrated in an educational plan, in order to get benefit from it. One in 6 patients on oral medication who practise SMBG neither use the results, nor tell their doctor about them (13). These findings demonstrate that glucose monitoring is a tool that helps to monitor diabetes status, facilitates management interventions (lifestyle changes, pharmacotherapy), but cannot be used without educational support.

In hospital settings, the standard glucose determination remains the central laboratory value. However, POC blood glucose measurement is now the standard bedside glucose monitoring technique in a variety of clinical settings including acute and chronic care facilities, general hospital wards and intensive care units, physicians' offices, nursing homes and assisted living facilities (14). In health care settings, patients have to be monitored before every meal or every 4-6 h if they do not receive nutrition. The frequency of blood glucose monitoring increases in patients on intravenous insulin infusion, ranging from every 30 min to every 2 h (9).

For adequate monitoring and therapeutic adjustments, SMBGs should provide accurate and reliable measurements. In the European Union, SMBGs that are intended to be used by patients with diabetes should meet the standard of the International Organization for Standardization (ISO) 15197, revised in 2013 (15). The evaluation of analytical performance according to ISO 15197 includes: evaluation of measurement precision, evaluation of system accuracy, eval-

uation of influence quantities (hematocrit and interfering substances such as medications), and evaluation of the stability of reagents and materials. According to the ISO 15197 minimum accuracy criteria, at least 95% of measurement results should fall within ±15 mg/dl of the reference value at BG concentrations <100 mg/dl and within ±15% at BG concentrations ≥100 mg/dl. Moreover, ISO 15197 requires the accuracy evaluation of 3 different test strip lots, and each individual test strip lot must comply with the 95% accuracy criteria.

The recently revised FDA guidance (16), published in 2016, for the premarket evaluation of SMBGs differs from ISO 15197 especially regarding system accuracy evaluation (Table 1). Ninety-five percent of all SMBG results should be within +/- 15% of the laboratory-based glucose results across the entire claimed measuring range of the device, and 99% of all SMBG results should be within +/- 20% of the laboratory-based glucose results across the entire claimed measuring range of the device.

Recommended standards of blood glucose monitoring test systems (BGMSs) designed for medical care settings differ from glucose meters used by people with diabetes at home (over the counter), and separate guidance has been issued by FDA. Thus, the standards of BGMS, used by health care providers in POC testing, are: • 95% of meter values should be within 12% of the reference value for BG over 75 mg/dl, and within 12 mg/dl for BG below 75 mg/dl; • 98% of values should be within 15% of the reference value for BG over 75 mg/dl, and within 15 mg/dl for BG below 75 mg/dl (17). BGMSs intended for prescription use in a hospital setting should be able to measure BG accurately down to 10 mg/dl and up to 500 mg/dl, while those intended for use outside a hospital setting should be able to measure BG accurately down to 20 mg/dl (17).

In a recent study, designed to evaluate the accuracy of 17 POC glucose meters, only 2 met the ISO 2013 criteria, and the mean absolute relative differences versus reference values ranged widely from 5.6% to 20.8% (18). Moreover, the price of the glucose strips did not correlate with the accuracy of the result (18). In another recent study, assessing the accuracy of the 18 most purchased personal blood glucose meters in USA, only 6 meters met the protocol-specified accuracy standard similar to current ISO and FDA standards, while the mean absolute relative differences versus reference values ranged from 5.3% to 15.5% (19). The surveillance of post-marketing device performance should be taken into consideration in the future. Over time, analytical accuracy might no longer represent the initial accuracy of data that were submitted to the regulatory authorities. The performance of blood glucose meters diminishes over time (19). However, the POC glucose meter technology is not always the cause of inaccuracy. Additional errors can come from: temperature, humidity,

Table 1. Minimum SMBG/BGMS system accuracy criteria according to ISO 15197/2003 and FDA/2016

	ISO 15197/2003		FDA/2016		FDA/2016			
% results	95% of SMBG results		95% of SMBG results	99% of SMBG results	95% of BGMS results		98% of BGMS results	
Within	± 15 |mg/dl	± 15 %	± 15 %	± 20 %	± 12 mg/dl	± 12 %	± 15 mg/dl	± 15 %
At BG	< 100 mg/dl	≥ 100 mg/dl	Entire range	Entire range	< 75 mg/dl	≥ 75 mg/dl	< 75 mg/dl	≥ 75 mg/dl

altitude, poor sampling and inappropriate strip storage and handling, patient's state or drug interference, sample sources and collection sites, interfering with the glucose meter cleaning solution or the disinfectant wipe (20). Safety standards should include interdiction of sharing lancing devices, needles or pens, to avoid the risk of blood-borne diseases (17).

Currently, POC blood glucose testing is the mainstay for monitoring and decision making in diabetes management. However, it cannot replace central laboratory testing for precision and accuracy. POC glucose meters are user friendly, with rapid turn-around times (<5 minutes), require small blood samples (0.3-1µl), and are cost-effective – a three times lower cost than central laboratory testing (17).

POC Continuous Glucose Monitoring Systems (CGMS) in diabetes management

Hypo- and hyperglycemia are common complications encountered in clinical care settings despite time and effort dedicated to achieving and maintaining good glycemic control. A target glucose range of 140–180 mg/dl is recommended for the majority of hospitalized patients (21). CGMS measure interstitial or venous glucose values with a frequency of 1 to 15 minutes and are closely correlated to plasma glucose values determined by central laboratories. An advantage of CGMS is represented by the alarms for either hypo- or hyperglycemia (22). Variations between interstitial and plasma values appear when there are rapid changes in plasma glucose levels. There are two types of CGMS: professional CGMS and real-time CGMS (Table 2). Professional devices are used for "blinded" or "masked" collection of glucose data. Patients wear the device for a specific time period, but only see the CGMS data after they have been analyzed by a healthcare professional. Personal CGMS can provide near real-time glucose data (rtCGM) or intermittently viewed data (iCGM). While rtCGM sends data continuously to a receiver, iCGM does not passively capture glucose information in the absence of a scan and the wearer must scan the sensor with a handheld reader in order for the sensor to initiate the real-time glucose measurements. The only iCGM is the recently approved form of CGMS known as "flash" glucose monitoring (FreeStyle Libre; Abbott) (23)

In terms of calibration, there are two kinds of sensors: those that are calibrated in the factory without the need of user calibration, and those that need calibration using capillary glucose values.

FreeStyle Libre Flash and FreeStyle Libre Pro do not need calibration by users. The calibration process is part of the sensor manufacturing process and performed under controlled laboratory conditions (23). However, a recent head-to-head accuracy comparison between the two newly approved Abbott FreeStyle Libre and Dexcom G5 Mobile systems showed that DG5M sensor has greater accuracy across all glucose values except in hypoglycemia, while Libre's accuracy decreases between days 11 and 14 (30).

The latest-generation CGMS are more accurate and sensitive for hypoglycemia. Thus, Guardian Paradigm Veo and MiniMed 640G developed by Medtronic allow the suspension of insulin infusion during or even prior to hypoglycemia (28), while the MiniMed 670G system automatically adjusts basal insulin levels. This kind of therapy is known as sensor-augmented insulin pump with low glucose suspend. The real-world trial data from the first 124 patients who completed 3 months of SmartGuard Auto Mode-enabled MiniMed 670G system use have been recently published. Real-world patients used Auto Mode for a median of 80.8% of the time. The overall mean time spent in target glucose range was 66% during baseline Manual Mode versus

Table 2. Professional and Personal devices specifications

Type of CGMS	Accuracy (MARD%)	Calibration (n/day)	Sensor life-time (days)	FDA approval	Ref.
Professional devices					
Roche iPro Professional	14.2	3	6	2016	[23]
Abbott FreeStyle Libre Pro	12,1	No	14	2016	[24]
Personal Devices					
DexcomG4 Platinum*	Adults: 13 Children: 15	2	7	2012	[25]
DexcomG5 Movile*	Adults: 9 Children: 10	2	7	2016	[26]
Medtronic Paradigm Veo	13.6	3	7	2006	[27]
MiniMed 640G System with SmartGuard	14.2	3	7	2017	[27]
Abbott FreeStyle Libre Flash	11.4	No	14	2018	[28]
FreeStyle Navigator II	12.3	5**	5	2011	[29]

*Approved for children
MDRD- the mean absolute relative difference per sensor
**FreeStyle Navigator II CGM system requires four calibrations on day 1 and one calibration on day 3.

73.3% during Auto Mode (P<0.001) (31).
Regarding long-term glycemic control, a recent study in 322 patients with T1DM showed a 0.5% reduction in HbA1c in patients following an intensive insulin regimen with CGM systems compared to those following the same intensive insulin regimen with SMBG (32). Two additional clinical trials in patients with T1DM showed that using CGMS along with multiple daily injections lowered HbA1c levels by 0.43% and 0.6%, respectively (33, 34).
Additional benefits of CGMS are reducing daily fluctuations of glucose levels. Thus, glycemic variability in type 1 DM patients using insulin pumps and real-time glucose monitoring devices had an SD reduction from 60.74 to 51.67 mg/dl (p=0.010), and AUC diminished from 41.23 to 21.22 (p<0.001) (35). Moreover, a recent study showed that integrated pump/CGMS technology versus multiple daily injections in T1DM increases life expectancy by 3.51 years (95% CI, 3.47–3.55) (36).
A recent study reported benefits of using flash CGMS even in well-controlled T1DM by reducing the time spent in hypoglycemia compared to using SMBG (37). Current guidelines have no specific recommendations for patients or for clinical setting use (38). However, support in selecting appropriate system for specific patient has been issued recently (39).
Several factors such as: edema, shock state, use of vasoconstrictors affect peripheral perfusion in ICU patients and disturb the accuracy of capillary glucose measurements (40, 41). Moreover, glucose measurement in ICU is performed intermittently with the risk of undetected hypoglycemia, and the workload for the ICU nursing staff is considerable (42). In this respect, several studies have shown that CGMS may guide insulin treatment in critically ill patients similarly to intermittent POC measurements.
The first-generation intravenous CGMS was evaluated in a multicenter observational study, in 100 critically-ill patients (43). The authors concluded that it was easy to set up and use, attached to a peripheral venous catheter. Of the intravenous glucose monitoring measurements, 93% met the 2003 ISO Standards for accura-

cy. Frequent and accurate POC blood glucose testing may improve the safety and efficacy of insulin therapy and blood glucose control in hospitalized patients (43).

A randomized controlled trial compared subcutaneous CGMS with frequent POC measurements in 156 critically ill patients (42). Subcutaneous CGMS were found to be as safe and effective as intermittent POC testing and reduced nursing workload and daily costs (42).

Another study compared subcutaneous and intravenous CGMS in 15 surgical patients, in operating rooms and intensive care units (3592 comparative samples). The intravenous CGMS STG-55 (Nikkiso, Tokyo, Japan) was defined as the standard device in the study, because it had previously shown acceptable accuracy compared to the blood gas analyzer (Pearson's correlation coefficient was 0.96) (44). The study found that subcutaneous and intravenous CGMS were not highly correlated during either surgery or ICU stay. The subcutaneous CGMS iPro2 (Medtronic Japan, Tokyo, Japan) was limited in terms of utility because it could not display real-time blood glucose levels (45). However, the authors did not deny the overall accuracy of subcutaneous CGMS, suggesting that blood glucose measurement during hemodynamic or fluid instability might be suitable for intravenous CGMS, while testing after stabilization might be suitable for the subcutaneous method (45).

POC HbA1c assays in diabetes management

Diabetes and prediabetes may be *screened and diagnosed* based on the same tests: plasma glucose levels (discussed above) or HbA1c levels (2). The HbA1c test has several advantages compared to plasma glucose criteria, including: fasting not required, better pre-analytical stability, and less variability during stress and illness. However, the lower sensitivity of HbA1c at the cut point of 6.5%, the greater cost and restricted availability of HbA1c testing in certain areas may offset the advantages. Moreover, it is important to take into consideration other factors that may impact hemoglobin glycation independently of glycaemia, including ethnicity, anemia, hemoglobinopathies, etc.

HbA1c testing should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) (www.ngsp.org) and standardized to the Diabetes Control and Complications Trial (DCCT) assay (2).

Although POC instruments are available for HbA1c testing, there are concerns that limit their diagnostic application, such as: differences in their accuracy, testing performed by non-laboratory personnel, and lack of a proficiency testing program. Although some POC HbA1c assays may be NGSP certified, the use of POC assays for diagnostic purposes is not generally recommended (9).

Recently, some authorities approved the use of POC HbA1c testing in particular settings. The Australian Government approved the use of the HbA1c test for diagnosis of the Indigenous Australian population enrolled exclusively in the QAAMS POC Testing Program. This decision was based on the consistently high analytical quality of POC HbA1c testing in QAAMS, as evidenced by the results of continuing external quality assurance and quality control testing over the past 15 years (46). DCA Vantage measured HbA1c values close to 6.5% both accurately and precisely. The authors argue that POC testing devices are suitable for the diagnosis of diabetes, and each individual POC device should be assessed independently when considering its suitability for diabetes diagnosis (46).

Conversely, POC HbA1c testing may be used for screening purposes. In a recent study, dental students were effective in screening patients in a dental school clinic for prediabetes or diabetes

by assessing conventional risk factors for diabetes, obtaining finger stick blood samples and analyzing the results with HbA1c test kits (47). Another recent study found that systematically screening adults (aged ≥45 years) for diabetes using a POC HbA1c test vs. standard practices greatly increases the chances for a screen to occur (P = 0.005). The authors concluded that POC HbA1c testing may be the most effective method to identify patients with unknown hyperglycemia (48).

HbA1c testing should be performed routinely in all diabetic patients during continuing care to assess glycemic control. The frequency of HbA1c testing depends on the achieved levels of HbA1c and their variability: at least two times a year in patients who meet treatment goals and every 3 months in patients who do not meet glycemic goals or whose therapy has changed (9). The American Diabetes Association recommends optimal HbA1c targets for non-pregnant adults less than 7%, but each target must be individualized to the particular patient (9).

The use of POC HbA1c testing may allow more timely treatment changes during consultations. Studies have found that patients who are aware of their HbA1c level have lower measurement results than those who are unaware; the availability of immediate results motivates patients for a better glycemic control (49). Only three POC HbA1c testing instruments are available in USA, having received NGSP manufacturer certification (Table 3) (50). Currently, NGSP requires at least 37 out of 40 samples to fall within 6%, making them precise and reliable for medical daily use (51). Moreover, these criteria will even be tightened starting with January 2019, as follows: 36 of 40 results within ± 5% (51).

POC HbA1c testing improved glycemic control by reducing HbA1c by 1.03 ± 0.33 percentage points during a period of 12 months in a clinical practice setting (52). Moreover, using one of these devices reduces health care costs, prevents complications and can improve patient's adherence (52).

Recently, a new HbA1c analyzer for POC testing was evaluated with a comparative laboratory instrument, in China. The sensitivity and specificity of HbA1c EZ 2.0 in the clinical diagnosis of diabetes was evaluated in 842 subjects from Beijing. At the HbA1c cut-off value of 6.5%, sen-

Table 3. POC HbA1c device features

Characteristic	HbA1C Now Chek Diagnostics (1)	Axis-Shield Afinion Analyzer (2)	Siemens DCA Vantage (3)
Physical size	Portable, handheld Dim:6.35/1.0/5.1 cm Weight: 0.18 kg	Bench-top unit Dim: 34/17/19 cm Weight: 5 kg	Bench-top unit Dim:27.7/25.4/28.7cm Weight: 3.88 kg
Sample size (µL)	5	1.5	1
Analysis time (min)	5	3	6
Reporting HbA1c range (%)	4–13	4–15	2.5–14
Other quantitative tests	No	Albumin: creatinine ratio C-reactive protein Cholesterol Creatinine	Albumin: creatinine ratio Microalbumin Creatinine

Bayer Diabetes Care A1cNow Monitor package insert. Sunnyvale, Calif, Bayer HealthCare, 2008. (2) Axis-Shield Afinion package insert. Dundee, Scotland, Axis-Shield POC, 2012. (3) Siemens DCA Systems package insert. Tarrytown, N.Y., Siemens Healthcare Diagnostics, August 2008.

sitivity and specificity were 76.1% and 86.6%, while the area under ROC curve for the clinical diagnosis of diabetes was 0.911 (53).

Limitations of HbA1c testing

Conditions that affect red blood cell turnover (anemia, recent blood transfusion, end-stage renal disease, pregnancy, use of drugs that stimulate erythropoiesis) may result in discrepancies between the HbA1c result and the patient's mean glycemia. Hemoglobin variants must be considered, particularly when the HbA1c result does not correlate with the patient's SMBG levels. Monitoring options in these cases include more frequent and/or different timing of SMBG or CGMS use. Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol are available, but their translation into average glucose levels and their prognostic significance are not as clear as for HbA1c.

HbA1c does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially patients with T1DM, glycemic control is best evaluated by the combined measurements of HbA1c and SMBG or CGMS. African Americans have higher HbA1c values compared to non-Hispanic whites for a given mean BG concentration (54).

POC tests for detecting microalbuminuria

Chronic kidney disease (CKD) is a chronic complication characterized by increased albuminuria, decreased glomerular filtration rate, or other kidney damage. The final evolution of diabetic CKD is end-stage renal disease requiring dialysis or kidney transplantation.

Screening for CKD in diabetic patients is done by measuring the albumin-creatinine ratio in spot urine collection. Measuring albumin alone, without simultaneously determining urinary creatinine, is susceptible to errors due to urine concentration variability.

The POC systems available for measuring urinary albumin and creatinine are: HemoCue® 201 urine albumin (Ängelholm, Sweden), URiSCAN 2 ACR (YD diagnostics, Yongin, Korea) and Clinitek® (Siemens® Medical Solutions Diagnostics, New York, USA). The HemoCue® system measures urine albumin quantitatively, using 18 µl of urine, and displays the result in 90 seconds. URiSCAN and Clinitek® systems are semi-quantitative POC tests for urinary albumin and creatinine measurements. In a controlled randomized clinical trial including 1020 samples, URiSCAN and Clinitek® had 90.2% and 83.0% sensitivity, and 87.7% and 72.2% specificity, respectively (55).

Nonetheless, urinary albumin POC systems are useful tools that provide immediate clinical information concerning renal status in clinical care settings. Future directions involve improving sensitivity and specificity for accurate diagnostic use.

Take home messages

POC devices are useful tools in clinical care settings for screening, diagnosis and management of diabetes, due to the following advantages:

- Fast sample-to-result test;
- Low sample consumption;
- Test results comparable to central laboratory findings;
- Non- or minimally invasive samples;
- Long shelf life with extended reagent storage;
- Easy system operation – can be used by patients or nurses;
- Cheap and portable systems.

Authors' contribution

AC (Conceptualization; Data curation; Formal analysis; Investigation;Methodology; Project administration; Writing – original draft)

CV (Data curation; Formal analysis; Investiga-

tion; Methodology; Writing – original draft)
AST (Conceptualization; Software)
AF (Conceptualization; Methodology; Supervision; Validation; Writing – review & editing)
Angela Cozma and Camelia Vonica have equal contribution to the paper.

Conflict of interest

None to declare.

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