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Critical Reviews in Clinical Laboratory Sciences

ISSN: 1040-8363 (Print) 1549-781X (Online) Journal homepage: www.tandfonline.com/journals/ilab20

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To cite this article: Guillaume Grzych, Inès Defauwes, Pascal de Tullio, Jean David Pekar, Thierry Brousseau, Giuseppe Lippi & Etienne Cavalier (2025) Blood glucose measurement inside and outside the laboratory: both preanalytical and analytical challenges, Critical Reviews in Clinical Laboratory Sciences, 62:8, 613-630, DOI: 10.1080/10408363.2025.2533855

To link to this article: https://doi.org/10.1080/10408363.2025.2533855

CRITICAL REVIEWS IN CLINICAL LABORATORY SCIENCES
2025, VOL. 62, NO. 8, 613–630
https://doi.org/10.1080/10408363.2025.2533855

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INVITED REVIEW

Blood glucose measurement inside and outside the laboratory: both preanalytical and analytical challenges

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ABSTRACT

Glucose measurement is a critical investigation in metabolic disease management, especially in diabetes and inherited disorders. However, both laboratory-based and handheld point-of-care (HPOC) (glucometers) glucose testing face significant preanalytical and analytical challenges. In central laboratories, glycolysis in uncentrifuged samples leads to glucose consumption, which may compromise diagnostic accuracy. Although sodium fluoride (NaF) is commonly used as a glycolysis inhibitor, it has a delayed effect, requiring several hours to stabilize glucose concentrations. Recently, citrate-buffered NaF-EDTA (FCE) tubes have been introduced to inhibit glycolysis more effectively, yet they remain underused. Preanalytical variables, including sample collection, transport, and processing delays, further impact glucose stability and the diagnosis of diabetes, including gestational diabetes mellitus (GDM). HPOC devices provide an alternative by delivering rapid results and minimizing preanalytical errors, but glucose meters are prone to physiological and analytical interferences, such as hematocrit variations, environmental conditions, presence of redox-active drugs, and enzymatic specificity issues. These interferences may lead to inaccurate glucose readings, impairing clinical decision-making, especially in intensive care and emergency settings. Moreover, discrepancies between capillary and venous glucose concentrations can contribute to misdiagnosis and inappropriate glycemic management. This review provides a comprehensive analysis of glucose measurement methodologies, their limitations, and potential improvements, emphasizing the need for preanalytical harmonization in laboratory testing and a better understanding of interferences in HPOC testing. Standardization of blood sample handling and adoption of optimized collection tubes could enhance glucose measurement reliability, ultimately improving diabetes diagnosis and patient outcomes.

ARTICLE HISTORY
Received 8 April 2025
Revised 27 June 2025
Accepted 10 July 2025

KEYWORDS
Glucose measurement; point-of-care testing (POCT;), preanalytical variability; glucose meters; analytical interference

Context and introduction

Accurate blood glucose measurement is essential in both emergency and routine clinical settings. Extreme fluctuations in blood glucose, whether hyperglycemia or hypoglycemia—require immediate medical intervention to prevent serious complications. Hyperglycemia is often accompanied by symptoms such as fatigue, excessive hunger and thirst, polyuria, and neurological abnormalities. If left untreated, it can lead to severe complications, including infections, neurological impairment, coma, and death [1]. Conversely, hypoglycemia can also have severe health consequences, with symptoms such as fatigue, mood disturbances, hunger, paraesthesia, nervousness, excessive sweating, tachycardia, and confusion. In extreme cases, profound hypoglycemia may also trigger seizures and coma [1] (Figure 1). Beyond these acute and potentially life-threatening conditions, glucose monitoring plays a crucial role in diagnosing pathological conditions such as diabetes (high glucose values) or inherited metabolic disorders (low glucose values) [2]. Glucose can conventionally be measured using different approaches, both in the central laboratory, at the bedside and by patient self-monitoring. Over time, various glucose measurement techniques have been developed, each with specific advantages and limitations, making their selection highly dependent on the clinical context. This

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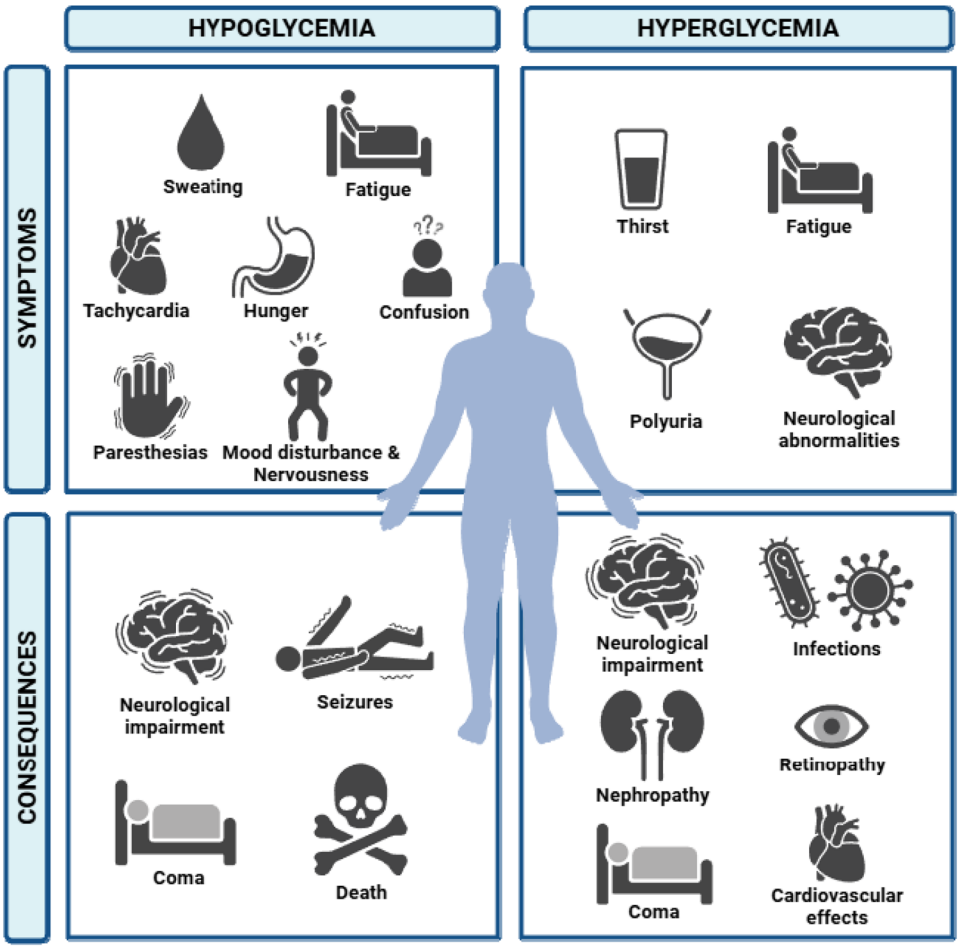

Figure 1. Symptoms and consequences of hypo- and hyperglycemia. Major clinical symptoms and potential complications associated with hypoglycemia and hyperglycemia. Recognizing these symptoms is crucial for timely diagnosis and intervention in both emergency and routine clinical settings.

review aims to provide a comprehensive overview of these methods, highlighting their respective strengths and weaknesses to guide their appropriate use in both laboratory and point-of-care settings.

Biological variation and analytical performance goals for glucose measurement

The assessment of biological variation (BV) is essential for establishing meaningful analytical performance specifications (APS) in laboratory medicine. The European Biological Variation Study (EuBIVAS) provided rigorously controlled data on glucose, reporting a within-subject coefficient of variation (CVI) of 4.7% and between-subject variation (CVG) of 8.1%, both notably lower than previously published estimates [3]. Based on these values, EuBIVAS recommends APS of ≤2.4% for imprecision (CVA) and ≤2.1% for bias standards that are more stringent than those proposed by Westgard in 2014 (CVA ≤2.8%, bias ≤2.3%) [4] or by the Clinical Laboratory Improvement Amendments (CLIA), which use broader criteria (±10% or ±0.33 mmol/L for glucose <5.6 mmol/L).

These EuBIVAS-derived APS are particularly relevant when measurements are used for diagnostic classification near defined thresholds, such as the 5.1 mmol/L fasting glucose threshold for gestational diabetes mellitus (GDM), based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) criteria. While not universally adopted, this cutoff illustrates how small analytical biases may influence patient categorization. For instance, values of 5.0 vs. 5.1 mmol/L may lead to different interpretations under HAPO-based guidelines, despite falling within the expected biological variation. The use of high-quality BV data is thus crucial to avoid misclassification and to support consistent, evidence-based clinical decisions.

This underscores the importance of harmonized, highly accurate glucose measurement methods, both in central laboratories and at the point of care.

Importantly, not all variations in glucose measurement will have the same clinical impact, as the

consequences largely depend on how the glucose value is used whether for acute therapeutic decisions, long-term glycemic monitoring, or diagnostic confirmation of conditions like diabetes or hypoglycemia. APS for glucose testing is influenced by the actual use of the test in a given clinical scenario.

Central laboratory assessment

From sample collection to final analysis, several methodological aspects must be considered to minimize errors and optimize diagnostic performance. This section explores the key principles of laboratory-based glucose testing, the methodologies employed, and the challenges associated with ensuring accuracy and reproducibility in clinical settings.

Methods

Although not used in routine clinical laboratories due to its complexity and cost, isotope dilution gas chromatography–mass spectrometry (ID-GC/MS) is recognized as a higher-order reference measurement procedure for glucose. This technique, developed in compliance with ISO 15195 and ISO 17025 standards and linked to NIST Standard Reference Materials (SRM 917), provides the highest level of metrological traceability. In the context of calibration and accuracy assessment of glucose measurement systems, the ID-GC/MS method has demonstrated a total measurement uncertainty of less than 2%, with excellent concordance to reference methods such as the PCA-hexokinase procedure. Its use ensures traceability to the "true" glucose value and supports harmonization efforts in laboratory medicine [4].

While such reference procedures define the analytical benchmark, routine glucose measurements in clinical laboratories rely on validated enzymatic methods compatible with automated analyzers. Three main techniques are commonly used for measuring glucose in central laboratories in multiparametric and blood gas analyzers. In multiparametric analyzer, the first method is spectrophotometric and uses the hexokinase enzyme. This method could be considered as the reference technique for measuring glucose in clinical laboratories [5]. In this method, glucose is converted into glucose-6-phosphate (G6P) generating ADP (Figure 2a). G6P then reacts with nicotinamide adenine dinucleotide phosphate (NADP), leading to generation of 6 phospho-gluconolactone and NADPH, a reaction catalyzed by the enzyme glucose dehydrogenase (GDH). The concentration of NADPH is then spectrophotometrically measured at 340 nm, and its absorbance is proportional to glucose [6].

The second method used in central laboratories is based on a colorimetric assay (Trinder), where the hydrogen peroxide (H_2O_2) generated by glucose oxidase (GOX) by glucose oxidation reacts with peroxidase in the presence of chromogenic substrates (4-aminophenazone and a phenolic compound) to form a quinoneimine dye. The absorbance of the dye is measured at 500–520 nm, and correlates with glucose concentration (Figure 2b) [7].

The third method used in central laboratories, nearly limited to blood gas analyzers, is based on electrochemical detection. Glucose is converted into 6 phospho-gluconolactone and oxygen (O_2), which is then simultaneously converted to H_2O_2 by the enzyme GOX. Oxidation of H_2O_2 finally produces an electric signal, whose magnitude is directly related to glucose [8] (Figure 2c). Glucose is measured using a fixed enzyme electrode, a cartridge, or a reagent cassette, primarily utilizing glucose oxidase [9].

Challenges and limitations

Both preanalytical and analytical factors can introduce variability, leading to discrepancies between measured and actual glucose statement [10]. Preanalytical challenges, such as patient statement (fasting, stress, medication) and sample statement such as glycolysis during sample transport, differences in blood collection tubes, and delays in processing, can significantly alter *in vitro* glucose concentrations before analysis. Analytical limitations, including interferences from endogenous and exogenous substances, as well as methodological differences between enzymatic and electrochemical techniques, can further impact result accuracy (Table 1).

This section explores these key issues, distinguishing between preanalytical pitfalls affecting glucose stability, analytical interferences that can compromise measurement precision in central laboratory settings, and finally clinical impact and related recommendations.

Preanalytical challenges

In vitro glycolysis and cellular glucose consumption. During sample transportation to the central laboratory, blood remains a "living medium" and glycolysis continues *in vitro*. A cellular consumption of glucose occurs, especially during the first few minutes after blood drawing. The term "artifactual hypoglycemia" has been proposed to define results of laboratory measurement which do not reflect the actual glucose concentration in the patient's sample, regardless of the presence of symptoms [11]. Early recognition is challenging, but is important to prevent anxiety and unnecessary treatment and diagnostic tests [12].

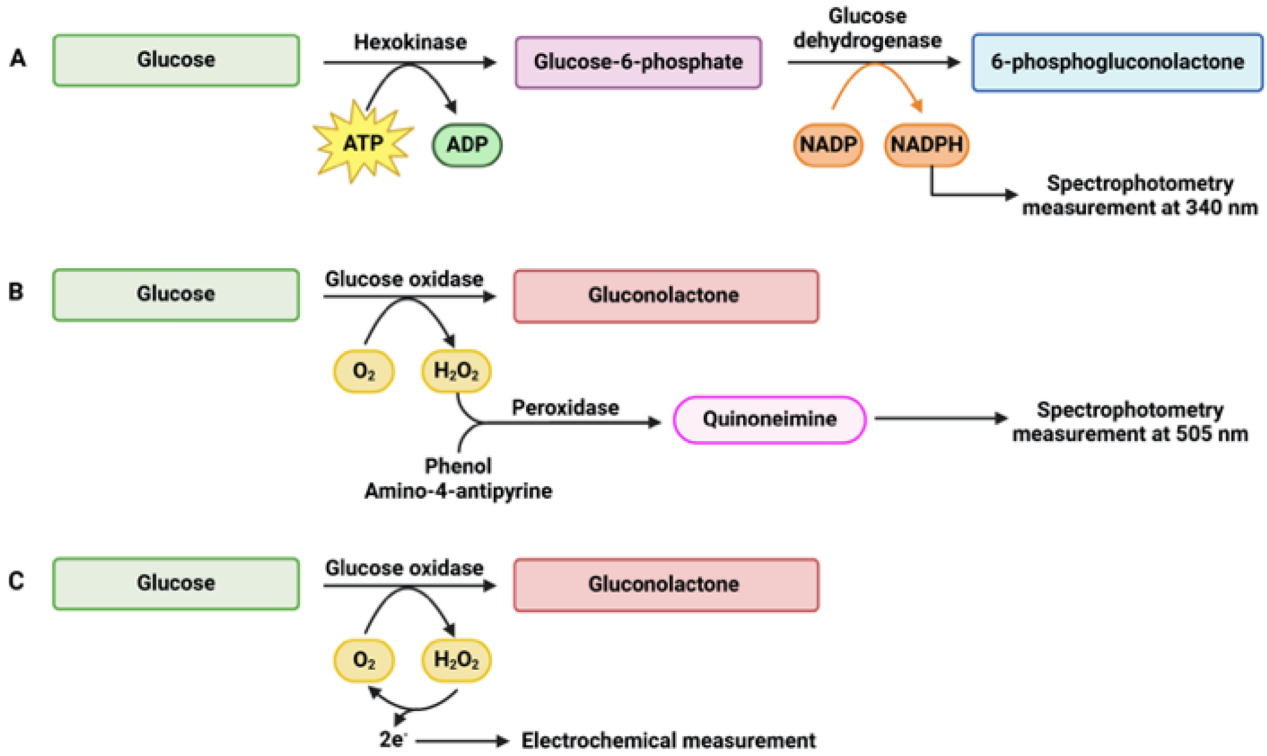

Figure 2. Glucose measurement methods used in the central laboratory; three main methods used for glucose quantification in central laboratories.
(a) Hexokinase-based enzymatic spectrophotometric method: Glucose is phosphorylated into glucose-6-phosphate (G6P) by hexokinase, leading to the reduction of NADP to NADPH via glucose-6-phosphate dehydrogenase. The concentration of NADPH is subsequently measured spectrophotometrically at 340 nm, providing a quantitative glucose assessment.
(b) Trinder colorimetric method using glucose oxidase and peroxidase: This approach relies on the oxidation of glucose by glucose oxidase (GOX) to generate H_2O_2, which reacts with peroxidase in the presence of chromogenic substrates (4-aminophenazone and a phenolic compound) to form a quinoneimine dye. The absorbance of the dye is measured at 500–520 nm, correlating with glucose concentration. This method is particularly susceptible to interferences from oxidizing and reducing agents such as ascorbic acid and uric acid.
(c) Electrochemical method using GOX: GOX catalyzes the oxidation of glucose to gluconolactone, generating hydrogen peroxide (H_2O_2), which is further oxidized, producing an electrical current proportional to glucose concentration. This method is commonly implemented in blood gas analyzers, offering high accuracy with reduced interference from hematocrit variations.

Table 1. Factors affecting blood glucose measurement accuracy.

Category	Examples/causes	Impact/notes
Pre-analytical	• Glycolysis during sample transport • Collection tube type • Delay in processing	Alters *in vitro* glucose before analysis
Analytical	• Endogenous substances • Exogenous interferences • Methodological differences (enzymatic vs electrochemical)	Can lead to inaccurate results depending on the method and sample matrix
Clinical relevance	• Use for acute decision-making • Diagnosis (e.g. diabetes, hypoglycemia) • Long-term monitoring	Some discrepancies have greater consequences depending on clinical use

The most used approach for preventing glucose consumption in blood samples is immediate separation of blood cells from serum or plasma by centrifugation and subsequent interposition of a physical barrier (which can be either a gel [13] or a mechanical device [14]) between blood cells and sample matrix. Indeed, recent studies have shown that the amount of glucose decrease into uncentrifuged blood tubes is associated with the leukocyte count, develops very early after blood drawing, may cause a high rate of spuriously low glucose values [15,16] and occurs also in sample with modest leukocytosis (i.e. ~15×10^6) [17].

When glycolysis is not rapidly inhibited, or when the blood cells are not quickly separated from the plasma [18], the glucose concentration decreases by 5 to 7% per hour in whole blood samples due to *in vitro* glycolysis [19]. The type of blood sample may influence this result, as it seems that serum may limit the availability of cells compared to plasma, which is linked to clot formation. Indeed, a study showed that glucose measurement in centrifuged serum gel tubes may be more clinically reliable, up to 96 h, compared to centrifuged lithium-heparin gel tubes stored at constant storage temperature [20]. Glucose concentration in lithium-heparin plasma began to decrease as early as 3 h after centrifugation, with a

continuous decline up to 96 h, often exceeding performance specifications between 6 and 24 h. In contrast, glucose in serum gel tubes only decreased significantly between 24 and 48 h but remained within performance specifications throughout the 96-h period, regardless of storage temperature. This was also confirmed by another study showing that, in samples centrifuged immediately after phlebotomy and stored at room temperature for 12 h, glucose concentration decreased by 34% and 14% in lithium-heparin tubes containing plasma and in serum tubes without gel separator, respectively [21]. Therefore, these studies highlighted better glucose stability in serum compared to plasma, likely due to a lower concentration of leukocytes in serum (may be due to clot formation, serum may limit the availability of cells compared to plasma), as these cells contribute to the acceleration of glycolysis [21].

Even in tubes containing a gel barrier, residual glycolytic activity may occur if centrifugation is suboptimal. Incomplete separation or entrapment of leukocytes and platelets within the gel interface can result in ongoing glucose consumption after centrifugation. Manufacturers recommend centrifuging gel tubes at 2000–3000 × *g* for at least 10 min at room temperature to ensure that cells migrate fully below the gel. If these conditions are not met, plasma may remain in partial contact with cellular elements. Consequently, several organizations such as the The American Diabetes Association (ADA**)**, World Health Organization (WHO) and International Federation of Clinical Chemistry **(**IFCC), Europrean Federation of Laboratory Medicine (EFLM**)** strongly recommend using venous plasma promptly separated **within** 30 min of collection, or collected into fluoride-citrate tubes when immediate centrifugation is not feasible, to ensure reliable glucose values and avoid spurious hypoglycemia due to glycolysis [22].

The World Health Organization (WHO) recommends separating the plasma quickly or placing the sample in an ice-water slurry, but this is often impractical in routine clinical practice [23].

Influence of blood collection tubes. A useful approach entails the use of additives containing a mixture of glycolysis inhibitors. when glycolysis is not rapidly inhibited or when the cells are not quickly separated from the plasma [18] (Figure 3). Several approaches have been explored to stabilize glucose concentration in blood tubes. The first significant innovation was the addition of sodium fluoride (NaF) in combination with potassium oxalate (KOx) as an anticoagulant [18]. This additive enabled better stabilization of glucose than using conventional serum and lithium-heparin blood tubes [18]. Fluoride acts by blocking the enzyme

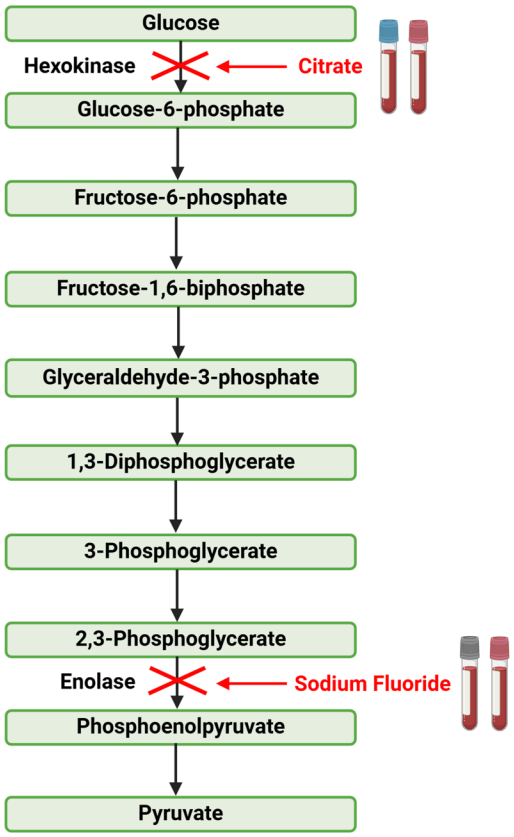

Figure 3. Main steps of glycolysis and effect of glycolysis inhibitors used in blood collection tubes. Key metabolic steps in glycolysis and sites of action of different glycolysis inhibitors used in blood collection tubes. Hexokinase inhibition by citrate: the initial phosphorylation of glucose to glucose-6-phosphate is pH-dependent. Citrate lowers the pH, inhibiting hexokinase and preventing the first step of glycolysis. Enolase inhibition by sodium fluoride (NaF): fluoride blocks enolase activity at a later stage of glycolysis, leading to incomplete glucose preservation if early steps remain active. Combined effect of citrate, fluoride, and EDTA (FCE tubes): by simultaneously inhibiting hexokinase and enolase while preventing blood coagulation, FCE tubes provide superior glycolysis inhibition, ensuring glucose stability over extended periods. The figure demonstrates how these inhibitors prevent progressive glucose degradation in uncentrifuged blood samples.

enolase (Figure 3), which plays a role in the later stages of the glycolytic process [18]. However, enzymes that act earlier in this metabolic pathway remain active and continue to consume glucose, which explains why the total inhibitory effect of fluoride takes approximately 4 h to become fully effective [18,24].

Despite these improvements, glucose degradation can still occur. It has been convincingly demonstrated that glycolysis may continue even when additives such as sodium fluoride or potassium oxalate are used. Since these compounds only inhibit the later stages of glycolysis (Enolase step, Figure 3), their effect is

delayed, and glucose underestimation has been clearly reported [25]. Notably, these additives could be in theory acceptable for measuring lactate due to their potent inhibitory activity on the enzyme enolase (Figure 3) [18].

A further advancement in blood glucose stabilization was achieved with the discovery that the enzyme hexokinase, involved at the first step of glycolysis, is only active at a pH of 5.9 or higher [18]. Thus, *in vitro* acidification of blood sample using a citrate buffer allows glycolysis to be inhibited at a much earlier stage than fluoride, ensuring faster glucose stabilization [18]. This approach also generates overestimation of glucose that would require the redefinition of additive-specific reference limits for plasma glucose [26–29]. Following this discovery, a new generation of blood tubes has been developed, containing three types of additives: citrate, which lowers pH and inhibits hexokinase; sodium fluoride (NaF), which blocks enolase; and ethylenediaminetetraacetic acid (EDTA), such as the Vacuette FCE Tube by Greiner Bio-One, which irreversibly prevents blood coagulation. It has been shown that such tubes containing citrate, NaF, and EDTA are effective in directly and completely inhibiting glycolysis, allowing glucose stability for up to 48 h at room temperature and 24 h at 37 °C, even in uncentrifuged tubes [24,30,31].

Some studies then show that glucose concentration in tubes containing citrate plasma is consistently higher than in those with fluoride plasma (+4.2%), lithium-heparin plasma (+4.2%), or serum (+9.8%) [18] or EDTA [19]. Additionally, glucose reduction in uncentrifuged or total blood samples stored at room temperature is lower with citrate buffer (0.9% at 2 h and 1.1% at 4 h), intermediate with NaF/KOx (6.1% at 2 h and 8.1% at 4 h), and almost linear in serum and lithium-heparin plasma [18] (4–5% per hour) [24]. These results should be considered on uncentrifuged whole blood but cannot be extrapolated to serum or plasma after centrifugation. Finally, in studies where samples were immediately centrifuged, glucose variation remained low after 4 h of storage at room temperature (between 0.7% and 1.3%), no matter the type of tube [18]. All types of tubes produced comparable results with immediate processing [19].

Temperature impact

It has been shown that placing samples at 4 °C before centrifugation only partially reduces the glycolysis process during the first 30 min after collection, even though this protocol is recommended by the WHO [23,32]. Ice slurry is used to slow down cellular metabolism through cooling. However, recent studies have shown that while rapid cooling can reduce the rate of glycolysis, it does not completely inhibit it, glucose in FCE tubes remained stable for up to 8.5 days at 4 °C (variation <0.26 mmol/L), but only 4 days at room temperature (18–22 °C), highlighting the significant impact of temperature on glycolysis inhibition and sample stability [32].

Although this may not be necessary for routine glucose testing due to typically short turnaround times and the transient nature of glycemia, long-term stability becomes relevant in situations such as delayed sample transport from remote or rural areas, sample batching, or retrospective studies.

Dilution impact

The use of a glycolysis inhibitor in granular rather than liquid form prevents dilution effects that may occur for insufficient filling of tubes containing liquid additives [33]. The introduction of a dilution factor related to liquid additive, seems these tubes less advantageous [31]. FCE tubes are provided with liquid additives (e.g. GlucoExact, Sarstedt, Nümbrecht, Germany), or with granulated additives (e.g. Vacuette FCE, Greiner Bio-One GmbH, Frickenhausen, Germany) [33].

On the other hand, when using tubes containing dry additives, the complete dissolution of these granular components can be challenging [33]. Incomplete dissolving of granular components or powder additives reduces glucose stability in non-centrifuged samples [33].

Hemolysis

Spurious hemolysis is a major issue in laboratory medicine, potentially biasing the results of many tests, including glucose measurement [18]. Hemolysis leads to the release of hexokinase into plasma, which can impair glucose measurement by artificially decreasing its concentration with the reference hexokinase-based assay [18,34]. The additives in blood collection tubes influence its occurrence [18]. Citrate buffer does not appear to induce more hemolysis than lithium-heparin plasma, which could explain why the concentration of glucose measured in citrate blood tubes is higher than in samples containing other additives [18]. However, NaF tubes show a higher frequency of hemolysis, affecting 94% of samples after 120 min, compared to only 19% with citrate buffer [18].

Additionally, the quality of sample for glucose analysis is also impacted by hemolysis because red blood cells contain lower glucose concentrations than plasma. This issue is further compounded by extended specimen transit times that lead to a delay in centrifugation and separation of plasma from blood cells. Spurious hemolysis happens when erythrocytes in whole blood specimens

lose their ability to maintain osmotic homeostasis resulting in cell lysis. This is due to the metabolic consumption of ATP reserves, which are finite ex vivo. Moreover, prolonged contact of erythrocytes with anti-glycolytic agents causes the release of intracellular fluid, free hemoglobin (Hb) and the enzyme catalase, which can further lower glucose concentration, this impairing the reliability of glucose analysis in specimens that are grossly hemolysed [32].

Icterus

Icterus can interfere with glucose measurement, particularly in methods that rely on colorimetric detection, such as glucose oxidase-peroxidase assays. In these methods, high bilirubin levels can react with hydrogen peroxide or chromogenic substrates, leading to falsely low glucose results. In contrast, enzymatic methods using hexokinase with NAD(P)H detection are generally less affected by bilirubin interference. The severity of the interference depends on the degree of icterus and the specific analytical technique employed [35].

Lipemia

Lipemia (lactescence) can interfere with glucose measurement, particularly in photometric assays. The turbidity caused by high concentrations of lipoproteins, such as chylomicrons and VLDL, scatters light and may lead to inaccurate absorbance readings, resulting in falsely low glucose values. Additionally, the volume displacement effect caused by the high lipid content can reduce the aqueous phase where glucose is measured, further contributing to underestimation. The extent of this interference depends on the assay method used hexokinase-based methods are generally less affected than glucose oxidase-peroxidase methods, especially those relying on absorbance in the visible range [36].

Analytical challenges

Gammopathies impact

Analytical interferences in glucose measurement have been reported in patients with monoclonal gammopathies, leading to pseudohypoglycemia [37,38]. This phenomenon occurs when monoclonal immunoglobulins, particularly IgM in Waldenström macroglobulinemia or IgG in multiple myeloma, interfere with glucose assays. The interference mechanisms vary depending on the analytical method used, but include increased sample viscosity, precipitation of proteins, and direct interactions with enzymatic reagents. In reported cases, patients with Waldenström's macroglobulinemia exhibited falsely low glucose due to protein aggregation during testing, leading to erroneous hypoglycemia readings. Similarly, in multiple myeloma, high immunoglobulin concentrations can interact with enzymatic glucose assays, altering the expected reaction and leading to falsely low values. These discrepancies between laboratory-based and point-of-care glucose measurements can result in misdiagnosis and inappropriate treatment, including unnecessary glucose administration. Clinicians should be aware of this potential interference, particularly in patients with plasma cell disorders, to ensure accurate glucose assessment and avoid inappropriate therapeutic interventions [38,39].

Electrochemical interference

One of the main limitations of the Trinder reaction used for glucose measurement (Figure 2b) is its susceptibility to interference from oxidizing and reducing agents, particularly ascorbic acid [40,41]. This method relies on glucose oxidase to produce hydrogen peroxide (H_2O_2), which, in the presence of peroxidase, reacts with 4-aminophenazone (4-AP) and a phenolic compound to form a quinoneimine dye detectable at 500–520 nm. However, ascorbic acid competes with the chromogenic reaction by reacting directly with H_2O_2, leading to peroxide depletion and reduced color formation. This interference is concentration-dependent, with studies showing that, at physiological levels (~65–110 µmol/L) [40], the effect remains limited, but at higher concentrations (>284 µmol/L), ascorbic acid can reduce glucose measurements by up to 11% using the Trinder assay. At extreme ascorbate concentrations (e.g. >2.2 mmol/L), as observed in patients taking high doses of vitamin C, glucose readings may be underestimated by more than 50%, leading to potential misdiagnosis of hypoglycemia [40]. The interference is time-dependent, causing a delay in chromophore development, which is particularly problematic in kinetic assays. While some commercial assays incorporate stabilizers or alternative chromogens to minimize this effect, significant analytical discrepancies remain, particularly in point-of-care settings where real-time accuracy is critical. Understanding and mitigating these interferences is crucial for improving the reliability of glucose measurements in both laboratory and clinical settings.

Global impact of blood glucose measurement bias on diagnosis and guidelines

The choice of blood collection tubes significantly impacts glucose, affecting patient classification. Traditional sodium fluoride (NaF) tubes have been widely used, but they have a delayed effect in inhibiting glycolysis, potentially leading to underestimation of glucose. In contrast, FCE offer superior glycolysis inhibition and maintain glucose stability for longer periods. For gestational diabetes

mellitus (GDM), the use of FC-Mix tubes could improve diagnostic accuracy by minimizing variability due to sample processing delays [42] but also could lead to overdiagnosis. ADA and WHO guidelines emphasize the importance of proper sample handling for glucose measurement, including immediate centrifugation or the use of citrate-buffered tubes [43,44]. However, the adoption of these tubes is limited by their availability and the need for standardized reference interval [45].

The impact of blood collection tube has been investigated within glucose concentrations and diagnostic outcomes during oral glucose tolerance test (OGTT) in 147 individuals, including 83 pregnant women [46]. FCE tubes showed significantly higher glucose than those with NaF alone. In this study, the comparator tubes containing NaF were not placed on ice and were not centrifuged within 30 min, which may have allowed glycolysis to occur, partially explaining the observed differences. This difference led to an increased number of diagnoses: at one center, GDM prevalence rose to 12.5%, and cases of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes mellitus (DM) increased to 36.7%, 6.7%, and 3.4%, respectively. However, a higher detection rate of glycemic disorders using FCE tubes does not necessarily equate to improved diagnostic accuracy. Earlier studies have pointed out that FCE tubes may increase glucose compared to current practice, potentially shifting the issue from underdiagnosis to overdiagnosis a concern that may also negatively impact patient outcomes. These findings confirm that citrate-containing tubes better inhibit glycolysis, but they also underscore the need to interpret results carefully. A study involving 157,415 hospital patients found that using FCE tubes resulted in glucose concentrations approximately 13% higher than those in fluoride tubes, leading to an estimated increase of 48.4–55.8% in patients classified as having impaired glucose according to WHO criteria [47]. This shift highlights the need for adjusted diagnostic thresholds when using newer tube types. Of 40 participants (20 healthy individuals and 20 patients with diagnosed diabetes mellitus), glucose concentrations were compared across five commonly used blood collection tubes. When measured 30 min after venipuncture, FCE tubes showed a more moderate but still clinically relevant bias of +3.2% in diabetics. Given diagnostic thresholds such as 7.0 mmol/L for fasting plasma glucose and 11.1 mmol/L for random/post-load glucose, this level of bias can lead to misclassification in up to 1 out of 5 patients near the threshold, particularly in screening for diabetes and GDM. The authors emphasize that citrate-buffered tubes are not interchangeable, and that diagnostic cutoffs must be validated locally for each tube type to avoid erroneous diagnoses and inappropriate management decisions [26]. A dual-center study compared glucose results from 16,840 samples of children and adolescents in Austria ($N = 10,590$) and Sweden ($N = 6,250$). Despite identical analytical protocols, a significant difference in glucose concentrations ($p < 0.001$) was observed. The root cause was identified as the blood collection tube type: lithium heparin (LH) in Salzburg vs. FCE in Uppsala [48]. A paired-tube comparison in 51 patients showed that LH tubes underestimated glucose values due to ongoing glycolysis, with a mean bias of −0.6 mmol/L, enough to shift patients across key diagnostic thresholds (e.g. IFG ≥5.6 mmol/L, diabetes ≥7.0 mmol/L). The authors emphasize that tube-related biases can distort epidemiological data, misclassify diabetes or IGT, and urge international harmonization of preanalytical procedures, particularly the use of NaF/C tubes, aligned with EFLM WG-PRE recommendations [18].

Analytical and preanalytical factors can significantly affect diabetes diagnosis near fixed thresholds. For example, Dickson et al. showed that the prevalence of GDM was 6.9% using the glucose oxidase method versus 5.1% with the hexokinase method, with only a 34% overlap in classified cases [49]. Similarly, Keutmann et al. demonstrated that the measurement uncertainty (MU) of plasma glucose assays can lead to misclassification near decision thresholds, recommending a maximum MU of 0.7 mmol/L for a fasting glucose of 7.0 mmol/L [50]. These findings underline the importance of incorporating biological variation and analytical performance criteria into diagnostic decision-making. We support the use of an "uncertainty zone" around fixed diagnostic cutoffs, particularly for OGTT results, where repeat measurements may be beneficial. To minimize misclassification risk, we recommend the use of venous plasma over serum, centrifugation within 30 min or use of glycolysis inhibitors, and validated, traceable analytical methods. These practices align with the guidance of the EFLM Working Group for the Preanalytical Phase (WG-PRE) [18].

The selection of appropriate blood collection tubes and adherence to international guidelines are hence essential for accurate glucose measurement and diabetes diagnosis. Further research is needed to standardize diagnostic thresholds for glucose when using citrate-buffered tubes, ensuring consistent patient classification and management across different healthcare settings. Due to the global lack of standardization in blood collection, transport, and centrifugation delays, diagnosing (gestational) diabetes based on glucose measurement remains insufficiently reliable [23,51]. Suboptimal preanalytical handling of plasma glucose measurements may lead to missed diagnoses of gestational diabetes. This general overview of the key challenges in central laboratory glucose assessment underscores the need for additional strategies to mitigate these issues. One

such approach involves bedside glucose measurement using handheld point-of-care devices.

Point-of-care assessment by glucometer

Handheld point-of-care (HPOC) glucose testing or glucometer has revolutionized diabetes management and intensive care unit by providing rapid, bedside measurements that facilitate immediate clinical decisions. Widely used in hospitals, outpatient settings, and home monitoring, these devices offer convenience and accessibility, reducing delays associated with laboratory-based testing. However, their accuracy and reliability can be influenced by multiple factors, including user technique, sample handling, and environmental conditions. Ensuring optimal performance requires a clear understanding of the principles underlying these devices, as well as the potential sources of measurement variability. This section explores the role of HPOC glucose testing in clinical practice, the methods employed, and the challenges associated with maintaining accuracy and standardization in diverse healthcare settings.

Methods

The general assumption underlying the potential usefulness of bedside glucose testing using POC devices is that this approach would actually eliminate most pre-analytical sources of variability and will enable obtaining faster results compared to central laboratory testing. Overall, capillary blood glucose assessment is a rapid method, which only needs a very limited amount of blood. It is hence especially useful for preventing important blood loss in patients needing frequent glucose monitoring (e.g. diabetics, neonates), as well as in those requiring fast results (i.e. intensive care unit or emergency department patients).

Glucose assessment by use of glucose meters usually entails an electrochemical reaction occurring on the electrodes of a test strips, followed by electron quantification, as summarized in Figure 2 [52]. Two enzymes are more wildly used in glucose meters, i.e. GDH and GOX. GDH catalyzes the oxidation of capillary blood glucose in gluconolactone (Figure 4a) with concomitant reduction of cofactor such as flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide

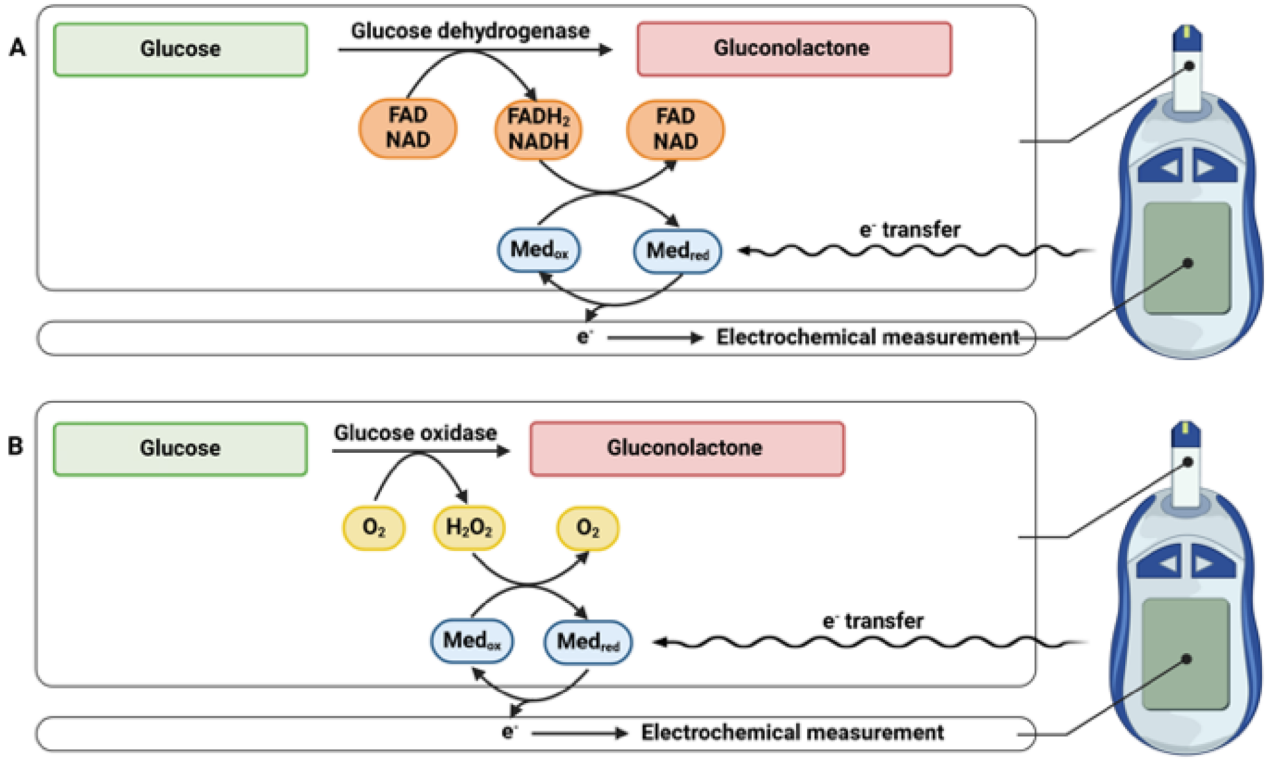

Figure 4. Point-of-care glucose measurement methods (glucometers).
Enzymatic reactions employed in point-of-care (POC) glucose meters. (a) Glucose dehydrogenase (GDH)-based electrochemical method: Glucose is oxidized to gluconolactone by GDH, which reduces a cofactor (flavin adenine dinucleotide [FAD], nicotinamide adenine dinucleotide [NAD]). The reduced cofactor then reduced the mediator (Med) which is then oxidized by electron transfer (from the glucometer) and generate an electrical current proportional to glucose concentration. (b) Glucose oxidase (GOX)-based electrochemical method: GOX catalyzes the oxidation of glucose to gluconolactone, with concomitant reduction of oxygen to hydrogen peroxide (H_2O_2). H_2O_2reduced the mediator (Med) which is then oxidized by electron transfer (from the glucometer) and generate an electrical current proportional to glucose concentration.
Both methodologies are widely used in POC devices, though GDH-based systems generally exhibit fewer interferences from oxygen fluctuations.

(NAD) and pyrroloquinoline quinone (PQQ) [53]. The reduced cofactor is then oxidized in the presence of a mediator, which is also oxidized at the electrode, thus generating an electric current directly proportional to glucose concentration in the test sample [53–55]. GOX catalyzes the oxidation of capillary blood glucose to 6 phospho-gluconolactone (Figure 4b) with concomitant reduction of O_2 in H_2O_2. H_2O_2 is then oxidized in presence of a reduced mediator (e.g. ferrocyanide) [54,56,57], which is oxidized at the electrode and generates an electric current directly proportional to glucose concentration in the test sample [55].

Measurement variability

Although the desirable analytical performance of glucose meters has been defined by many worldwide panels, definitive consensus has not been reached so far. According to the International Organization for Standardization (ISO) 15197 (requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus) document [58], the acceptable inaccuracy for 95% of the measures is 15 mg/dL (0.83 mmol/L) for glucose values <100 mg/dL (<5.55 mmol/L). For glucose values >100 mg/dL (i.e. >5.55 mmol/L), 15% is the maximum allowed inaccuracy for 95% of the measures [59,60]. Interestingly, the ADA has set a much more narrow limit of 5% inaccuracy, regardless of glucose values [61].

A recent review article has analyzed the results of 58 studies published between the years 2010 and 2017, based on as many as 143 different glucose meters [62]. Overall, 73% and 23% glucose meters commercialized before and after 2014, respectively were found to be non-compliant with the ISO 15197 in at least one study [62]. A further analysis revealed that noncompliance with ISO 15197 in at least one study was as high as 36% and 68% for glucose meters using GDH or GOX, respectively. Repeatability studies using a pool of blood samples tested on 5 different glucose meters (4 using GDH and 1 using GOX) showed an overall daily variation comprised between 1.1% and 7.7% [63].

Performance studies are usually based on comparison of capillary blood glucose with serum or plasma glucose measured with a reference laboratory technique. Using different types of glucose meters in the same laboratory, the variations among measurements could easily exceed the desirable specifications, thus justifying the need to implement a reliable external quality assessment (EQA) scheme. Interestingly, Bietenbeck et al. recently reported that the percentage of unacceptable EQA data was >10% in Germany, and was more accentuated in samples with low glucose values [64].

Limitations

Although the optimal accuracy of glucometer results shall be maintained within $a \pm 15\%$ limit according to the recent ISO recommendations, some sources of interference may jeopardize the quality of testing far beyond this threshold. The most frequent causes of interference can be basically classified as preanalytical, physiological, electrochemical, competitive, and environmental. For preventing or limiting the health risk of artefactual results, glucose monitor users shall always be informed on the various sources of possible interference in glucose measurement.

POCT in intensive care units: clinical implications and controversies

The clinical use of point-of-care glucose devices in intensive care units (ICUs) has been the subject of extensive debate. A study demonstrated that tight glycaemic control (target 80–110 mg/dL) improved clinical outcomes in critically ill patients [65]. However, these findings were challenged by the multicenter NICE-SUGAR trial [66], which reported increased mortality associated with intensive glycaemic control, largely due to hypoglycemic events. Subsequent analyses have raised concerns about the accuracy of POCT glucose meters in ICU settings. Cembrowski hypothesized that variations in hematocrit levels frequent in ICU patients may have biased glucose meter results [67], leading to inappropriate insulin administration. Van den Berghe, who led the original Leuven trial, recently summarized two decades of evidence [68], highlighting the complexity of implementing safe glycaemic control protocols in critical care. In ICU patients, physiological and technical factors such as peripheral vasoconstriction, low oxygen saturation, hemodynamic instability, and sample matrix differences (capillary vs. arterial vs. venous blood) contribute to POCT measurement variability. These issues underline the necessity of correlating POCT readings with laboratory-based or blood gas analyzer measurements, especially when critical therapeutic decisions are at stake.

As a result, most international guidelines now advocate for a cautious interpretation of POCT results in the ICU, and emphasize the need for method validation, confirmatory testing, and device calibration in these high-risk settings.

Pre-analytical interferences

During capillary blood collection, some substances present at the skin surface may generate interference in glucose measurement. Alcohol used as disinfectant

may be one of such cases. In patients with certain diseases, such as Raynaud syndrome, vasoconstriction can reduce capillary blood flow. Misuses of glucose meters (e.g. using wrong strips or non-optimal strips filling) can also lead to unreliable data or error messages. Strips conditioning is a well-known source of measurement bias. A recent study described a risk as high as 45% of bacterial contamination when using test strips packed in multi-use vials compared to a much lower 7% bacterial contamination for single-use packets [69]. Mistakes in result interpretation can also occur due to erroneous reading by insufficiently trained operators or confuse displays (for example: unit or decimal reading error) [70].

Physiological interferences

Some physiological conditions could also have an impact on glucose meter values. Among these, hematocrit interference is probably the best known. Basically, a high hematocrit value is accompanied by enhanced blood viscosity, which may then interfere with capillary blood glucose measurement, typically causing artefactual hypoglycemia [71]. Conversely, low hematocrit values may be associated with overestimation of capillary blood glucose for the opposite reasons [72] (Table 2).

The pH value may interfere with the redox potential of electrochemical reaction occurring on the test strip. Therefore, pH variations induce changes on cofactors and mediator oxidation, thus ultimately modifying electrons release and current measured in the test system [63]. Overall, a pH increase can hence promote overestimation of capillary blood glucose, whilst glucose can be underestimated in the presence of acidosis (Table 2). Notably, this type of interference varies among the different devices and is usually detectable in samples with high glucose values [63], since many glucose meters are now equipped with reagents which effectively neutralize the effect of pH. Changes in Oxygen Partial Pressure (pO_2) can also impact capillary blood glucose assessment. In particular, high pO_2 may cause glucose underestimation [73], and this evidence shall hence raise alertness that spurious glucose readings may occur in patients undergoing oxygen therapy [52].

Electrochemical interferences

Glucose redox potential is the basis of capillary blood glucose measurement. Molecules such as ascorbic acid, dopamine, and acetaminophen also have redox potential which can interfere with capillary blood glucose measurement. In the presence of these substances, the electric current generated on the test strips can be higher, thus leading to overestimation of the real glucose value.

The antioxidant properties of ascorbic acid are largely used for decreasing capillary permeability and fluid needs in burnt patients admitted to the intensive care units [74]. In these patients, hyperglycemia induces muscle catabolism, decreased immune function, and endothelial dysfunction, often leading to skin graft rejection [75]. Therefore, insulin is a frequent therapeutic choice in these patients, in order to prevent hyperglycemia and its complications. Since high levels of ascorbic acid are associated with overestimation of capillary blood glucose measured with glucose meters [72,76], this potential interference may lead to substantial insulin therapy errors, which would ultimately jeopardize the therapeutic management of these critical patients. Notably, intravenous injection of ascorbic acid in association with corticosteroid an thiamin are also used in intensive care units for reducing mortality of severe sepsis and septic shock, and they could further rise the risk of analytical interference [77]. The underlying basis of ascorbate interference involves ascorbic acid oxidation, which is then associated with electron release and generation of electric current [76], ultimately accounting for spurious elevation of the real glucose concentration. Similar mechanisms have been described for both acetaminophen and dopamine, since oxidation of free thiol group leads to enhanced electron release and glucose

Table 2. Known interferences for capillary blood glucose meters.

Interference type	Interfering factor	Glucose measurement variation	References
Physiological interferences	Hematocrit	↓ Hematocrit → ↑ glycemia ↑ Hematocrit → ↓ glycemia	[57,59,71,72,82,104–107]
	pH	↑ pH → ↑ glycemia ↓ pH → ↓ glycemia	[63,73]
	pO_2	↑ pO_2 → ↓ glycemia	[52,73]
Drug interferences	Ascorbic acid	↑ Interfering factor → ↑ glycemia	[53,59,72,75–77,82,106]
	Acetaminophen		[59,72,76,108]
	Dopamin		[72,76]
	Maltose / Icodextrin	↑ Interfering factor → ↑ glycemia	[59,72,81,82]
	Galactose		[59,72,81]
Environmental interferences	Temperature Humidity	Extreme temperature and/or humidity → unpredictable variation	[52,73]
	Altitude	↑ Altitude → ↑ glycemia	

overestimation (Figure 4) [76,78,79]. Notably, these sources of interference can be frequently observed also in samples with low glucose values [72,76].

CGM and HbA1c discordance

While CGM provides real-time information on glycaemic excursions and time in range, laboratory HbA1c remains the gold standard for long-term glycaemic control assessment. However, discrepancies between CGM-derived average glucose and measured HbA1c are frequently observed. These mismatches can result from altered red blood cell lifespan (e.g. anemia, hemoglobinopathies, iron deficiency), which impacts the degree of hemoglobin glycation independently of glucose exposure. Additionally, interindividual variability in glycation rates can lead to significant differences in HbA1c for the same mean glucose level. Lenters-Westra [80] demonstrated that such discordances may affect up to 20% of diabetic patients, potentially leading to misinterpretation of glycaemic control if HbA1c is used in isolation. This underscores the need to interpret HbA1c results alongside CGM data, especially in patients with conditions known to alter erythrocyte turnover or glycation efficiency.

Competitive interferences

Some carbohydrates such as maltose, icodextrin, and galactose have a molecular structure resembling that of glucose, and hence potentially generating interference in glucose meter readings. Basically, free reduced groups on glucose (and structurally-related molecules) react on the test strip, with generation of electrons and electric current [81]. Icodextrin, used for peritoneal dialysis, is a polymer metabolized by amylase in oligosaccharides (maltose and maltotriose) [81], which hence generates an interference similar to that of maltose, which is a disaccharide composed by two glucose molecules. Galactose is a monosaccharide with a free reduced group reacting like glucose [81]. All these compounds, when present at high concentration, would hence generate variable extents of overestimation of capillary blood glucose [72,82].

Environmental interferences

Environmental factors can also have an impact on glucose meter readings (Table 2). Basically, temperature and humidity may both modify the activity of the enzymes on the test strip, thus biasing glucose measurements [73]. Enzymes can be denaturized and inactivated by extreme temperatures, whilst humidity can cause early rehydration of dry reagents on the test strip, thus interfering with enzyme activity [52]. Unfortunately, the direction of the glucose variation (i.e. increase or decrease) is often unpredictable. Finally, altitude has been reported as another important factor which may generate a bias in glucose meter reading, due to the effect of hypoxia present at high altitudes [52,73].

Clinical implications

The various sources of interference that have been discussed in the previous parts of this article can effectively generate a bias in glucose measurement, but this variation does not necessarily produce a significant clinical impact. Some methods have hence been proposed to estimate the clinical impact of these sources of variation in glucose measurement [83,84].

Clarke et al. have developed a diagram based on an error grid analysis, aimed at evaluating the clinical significance of difference between glucose values measured in capillary blood by glucose meters and in venous blood with the reference central laboratory technique [83]. Five precision zones were constructed, as shown in Figure 5. When the difference between the glucose meter and the reference laboratory method is within zone A and B, the risk of adverse impact on clinical and therapeutic management is mostly insignificant [73,83]. Conversely, when the difference is located within the zones C, D, and E, adverse clinical consequences may potentially develop. In particular, a bias located within the zone E means that the difference between the two values is so wide, that the managed care can be dramatically affected, even generating a life-threatening risk for patients [83].

Another diagram has been developed, called Parkes Grid Analysis (Figure 5). This is basically a modified Clarke's diagram, adapted for avoiding discontinuity between risk zones in which low measure variations can cause important risk modifications [84]. Parkes Grid analysis is hence more specific for diabetic patients (for both type 1 and 2 diabetes). According to a study carried out in New Zealand, including 100 diabetic patients whose glucose values were measured with 3 different GDH glucose meters, 98–99% of the glucose measures were found to be in zone A and 1–2% in zone B, respectively. In the second part of the study, including 146 patients (140 diabetics and 6 non-diabetics) whose glucose was measured with 3 different GDH glucose meters and 2 different GOX glucose meters, 79–100% of the glucose measures were found to be in zone A and 0–21% in zone B, respectively (Figure 5). Notably, no measure fell in zones C, D, or E for any of the glucose meters tested. It was hence concluded that, according to the results of the study, glucose meter accuracy was safe enough for guiding therapy [85,86].

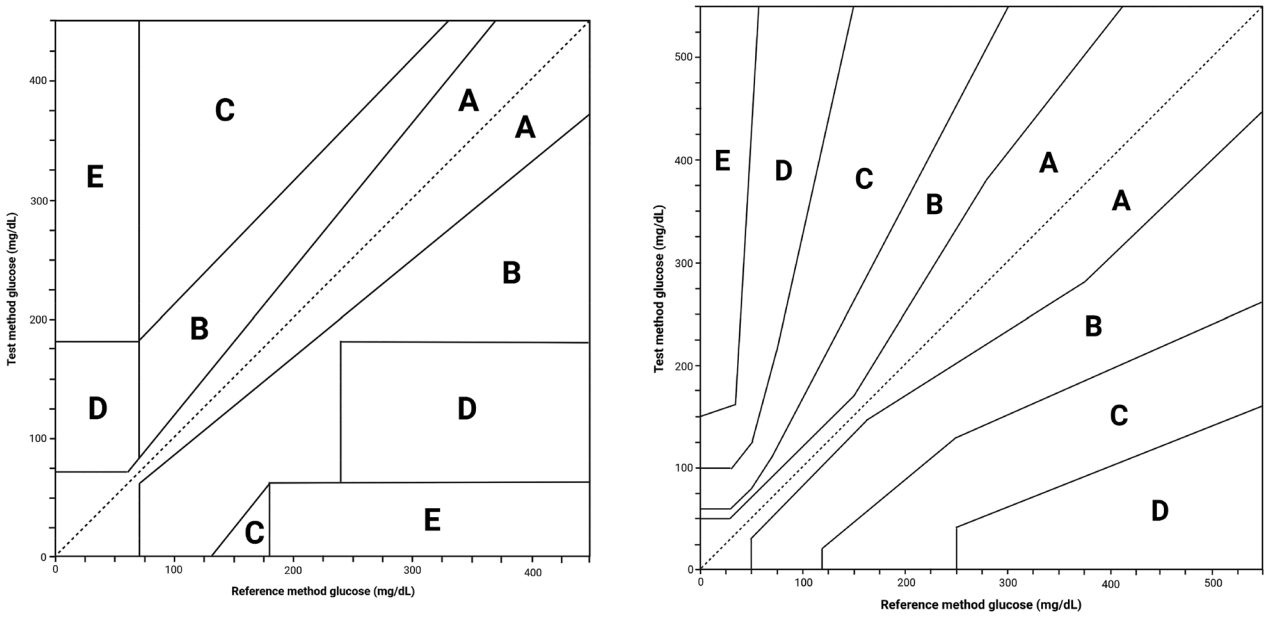

Figure 5. Clarke Error Grid and Parkes Grid Analysis for glucose measurement accuracy evaluation. These diagrams are used to assess the clinical impact of discrepancies between glucose values obtained from point-of-care devices and those measured in reference laboratory methods.
Left: Clarke Error Grid Analysis: This model classifies glucose measurement errors into five zones: Zone A: Clinically acceptable variations with no impact on medical decisions. Zone B: Deviations that are unlikely to significantly affect patient management. Zone C: Errors that could lead to unnecessary interventions. Zone D: Errors with a high risk of causing incorrect clinical decisions. Zone E: Severe errors that could result in life-threatening consequences [102].
Right: Parkes Grid Analysis: An adapted version of Clarke's model designed specifically for diabetic patients, with continuous risk zones rather than discrete regions, improving accuracy in classifying measurement errors. The use of these grids is essential for evaluating glucose meter performance and ensuring patient safety in clinical practice [103].

Several studies have demonstrated that high doses of antioxidants, particularly vitamin C, can cause significant interferences in glucose meters, leading to pseudohyperglycemia. A study showed that ascorbic acid led to falsely elevated glucose values in hospital-use HPOC notably the Roche Accu-Chek Inform II, resulting in inappropriate insulin administration [87]. A controlled *ex vivo* study showed that vitamin C, N-acetylcysteine (NAC), and glutathione caused clinically significant overestimations on several commercial glucose meters, with up to 23.5% of values falling in risk zone C and more than 10% in zones D or E of the Parkes error grid—indicating a high risk of inappropriate medical decisions [78]. A concentrations of 2,0 mmol/L vitamin C caused unacceptable bias in Accu-Chek Inform II and HemoCue devices, mimicking glucose in an equimolar fashion, particularly in patients with renal failure receiving IV vitamin C [88]. Together, these studies highlight the urgent need to identify and monitor potential interferences in glucose meters use, especially in critical care settings.

Technological advancements and embedded corrections in modern glucose meters

Point-of-care devices have significantly improved in terms of analytical robustness through the integration of real-time correction algorithms. Devices like the StatStrip® Glucose Hospital Meter (Nova Biomedical) incorporate direct hematocrit measurement *via* dedicated electrodes and apply internal corrections, enabling accurate results across a wide hematocrit range (20–65%) without manual adjustments [57]. This is especially relevant in neonatal and critically ill patients, where hematocrit variations are common [89].

Additionally, newer HPOC systems have integrated detection and compensation mechanisms for interfering substances, including ascorbic acid, maltose, uric acid, and galactose [78,90]. These improvements are achieved through enzyme-specific shielding, dual-channel biosensors, or redox-mediator modulation [78]. However, performance remains device-dependent, and verification with reference laboratory methods is still recommended in cases of clinical discordance.

Continuous glucose monitoring: strengths and limitations in clinical practice

Continuous glucose monitoring (CGM) systems provide near real-time tracking of glucose trends by measuring interstitial glucose concentrations *via* subcutaneous sensors. This technology has significantly improved glycemic control and reduced hypoglycemic episodes, especially in patients with type 1 diabetes [91], and is now increasingly used in type 2 diabetes [92,93] and

during pregnancy [94]. However, interstitial glucose does not reflect plasma glucose instantaneously. A physiological lag of 5 to 15 min exists, which becomes clinically relevant in rapidly changing glycemic conditions, such as during hypoglycemia, insulin boluses, or acute illness [95].

CGM accuracy is typically assessed by the Mean Absolute Relative Difference (MARD), with modern systems reporting MARDs between 8% and 13%, depending on the model and patient population [96]. Although recent advances have improved sensor reliability, CGM is not yet validated for glucose-based decision-making in acute care settings, such as intensive care units or emergency departments [97,98], where rapid and precise capillary or plasma glucose assessments remain the gold standard. Moreover, CGM accuracy may be affected by perfusion changes, edema, or vasoconstriction, all common in critical illness [99].

Therefore, while CGM offers substantial advantages for long-term glucose management, its use should be considered complementary rather than substitutive to POCT or central lab measurement in acute or diagnostic contexts. This review underscores the need to match the method of glucose assessment to the clinical setting and patient condition.

Artificial intelligence and future perspectives

Artificial intelligence (AI) is increasingly used to enhance CGM interpretation and glucose control. Closed-loop systems combining CGM with Bluetooth-connected insulin pumps now integrate reinforcement learning algorithms capable of adjusting insulin delivery in real time, based on dynamic glycaemic trends [100]. Additionally, machine learning models, including neural networks and random forests, are being applied to noninvasive technologies such as near-infrared or Raman spectroscopy for continuous glucose estimation [101]. These advances mark a transition toward more autonomous, precise, and patient-friendly glucose monitoring strategies.

Troubleshooting guide in case of glucose value discrepancies between laboratory, blood gas analyzer, and POCT glucometer

When multiple glucose measurement methods are available within the same institution such as central laboratory analyzers, blood gas analyzers, and HPOC devices, clinicians may occasionally face discrepancies between values obtained from these different platforms. These discordances can stem from preanalytical delays, matrix differences (e.g. capillary vs. venous), physiological factors, or method-specific interferences. Understanding the origin of such mismatches is essential to avoid misinterpretation and inappropriate therapeutic decisions, particularly in emergency or critical care settings. To assist in this process, Table 3 summarizes common discrepancy scenarios, their likely causes, and recommended troubleshooting actions. This practical guide is intended to support clinicians and laboratory professionals in identifying, interpreting, and resolving glucose measurement inconsistencies in daily practice.

Table 3. Troubleshooting guide in case of glucose value discrepancies between laboratory, blood gas analyzer, and POCT glucometer.

Observed discrepancy	Suspected cause	Suggested action
HPOC glucose ≫ Lab glucose	Reducing substance interference (e.g. vitamin C, dopamine)	Review patient treatment, retest using lab method
Lab glucose < HPOC	Glycolysis due to delayed processing of lab sample	Check sample type/tube, verify processing delay
HPOC glucose ≪ lab glucose	High hematocrit or sensor strip defect	Confirm with venous sample, calibrate or change device
All values discordant in unstable patient	Rapid glucose fluctuation, different matrices (capillary/plasma)	Repeat test on venous sample, interpret with clinical data

Conclusions

The measurement of glucose, whether performed in central laboratories or at the POC, remains vulnerable to several preanalytical and analytical challenges that can impact accuracy and clinical decision-making. Although not yet routinely implemented, techniques such as nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS) may offer high-specificity glucose quantification with minimal redox interference, opening future perspectives for critical applications. While laboratory-based testing ensures high precision, it is highly dependent on proper sample handling to prevent glycolysis-related glucose degradation, whereas HPOC testing provides rapid results but remains vulnerable to physiological and environmental interferences. Future developments should focus on improving blood collection strategies, particularly through wider adoption of FCE tubes, which offer better glucose stabilization compared to traditional fluoride tubes, though their integration into clinical practice would require standardized diagnostic thresholds. Automation in sample transport, immediate centrifugation, and implementation of artificial intelligence for interference detection could further enhance accuracy and reproducibility in glucose measurement. Advances in HPOC devices, including next-generation

biosensors with improved enzymatic specificity and automatic correction algorithms, are also promising for reducing measurement errors. Moreover, the harmonization of international guidelines by scientific societies such as the ADA, WHO, EFLM, and IFCC remains essential to ensure consistency in glucose measurement methodologies and diagnostic thresholds across different healthcare settings. The growing field of CGM and implantable sensors could also complement conventional laboratory testing, enabling a more dynamic and personalized approach to glucose management, particularly for diabetic patients and critically ill individuals. Ultimately, addressing these challenges through technological innovation and standardized protocols will be key to improving diagnostic reliability and optimizing patient outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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