How accurately do we measure blood glucose levels in intensive care unit (ICU) patients?

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Hyperglycaemia is commonly found in critically ill patients as a result of numerous processes such as increased gluconeogenesis and glycogenolysis caused by elevated levels of corresponding hormones and insulin resistance. As the clinical consequence of hyperglycaemia has been shown to increase morbidity and mortality in various clinical settings, many hospitals by now use tight glycaemic control protocols for their patients in intensive care units to maintain normoglycaemia. The success of intensive insulin therapy depends crucially on frequent and accurate blood glucose measurements with immediate feedback of results. Therefore, in almost all cases, this will be done by point-of-care testing methods, raising the question of how accurately blood glucose levels are actually measured and what devices should be used. This review focuses on glucose assay principles, specimen matrices, influences and interferences of glucose measurements and finally looks at the numerous evaluation reports on point-of-care glucose testing devices.

Since the first publication by van den Berghe et al. on the significant reduction of morbidity and mortality among critically ill patients in a surgical intensive care unit by intensive insulin therapy, other studies have been examining this protocol in various settings. These trials have reported inconsistent effects on mortality and on increased rates of severe hypoglycaemia. Despite conflicting evidence, intensive insulin therapy has been recommended as the standard of care for critically ill
patients by the American Diabetes Association,7 the American Association of Clinical Endocrinologists8 and the Surviving Sepsis Campaign.9 Two meta-analyses were published with data from 29 randomised controlled trials10 and data from 26 trials,11 including the recent NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation) study.12 Both showed a similar overall pooled estimate of effect on mortality, concluding that such therapy did not reduce mortality among critically ill patients. However, the meta-analysis by Griesdale et al.11 showed a clear benefit among surgical ICU patients. Furthermore, intensive insulin therapy significantly increased the overall risk of hypoglycaemia by sixfold11 and fivefold,10 regardless of the ICU setting. In their summary, Griesdale et al.11 conclude that “some patients may benefit from intensive insulin therapy, although the characteristics of such patients remain to be clearly defined; as does the effect of different blood glucose algorithms, the method of measuring blood glucose and the influence of nutritional strategies.” While data about the beneficial effects of tight glycaemic control in critically ill patients may still be conflicting and inconsistent,2–6,10,11,13–16 the importance of a reliable and fast determination of blood glucose levels cannot be undermined. Accurate and precise glucose measurements are one of the most important prerequisites for achieving tight glycaemic control without increasing the risk of hypoglycaemic episodes.11,17–20 Boyd et al.21 published a study on the effects of glucose meter imprecision and inaccuracy on the administered dose of insulin for two insulin administration algorithms. The Monte Carlo simulation model applied clearly demonstrated a direct relationship between the total error of meters and the rate of incorrect insulin dosages by either algorithm. In conclusion, glucose meters that achieve both a CV and a bias <5–6% rarely lead to major errors in insulin dose. A simulated total analytical error of 5% led to incorrect insulin doses in 8–23% of cases, whereas total analytical error of 10% led to incorrect insulin doses in 16–45% of cases. In order to provide 95% correct insulin dosing, both the bias and imprecision of the meter had to be <2%. One (theoretical) limitation of this study is however that it does not address the importance of frequency of glucose measurements, as random errors are probably of little consequences when glucose measurements are repeated several times per hour.

Assay principles

Different techniques are being used for the quantification of glucose, including highly sophisticated methods such as mass spectrometry and infrared spectroscopy. Yet/However Routine analysis methods applied in central laboratories analysers, in POCT devices for use in hospitals and outpatient clinic settings and even in the homecare glucose meters for patient self-testing are all principally based on enzymatic methods. Basically, the specificity for measuring glucose is achieved by one of the three enzymes, glucose oxidase (GO), glucose dehydrogenase (GDH) or hexokinase. To understand the many interferences and influences on glucose measurements by different devices, one has to understand the basic chemistry of these reactions and even the side reactions, as they may cause two meters with even the same enzyme to have different interferences.

**Glucose oxidase (GO)** requires both water and oxygen to oxidise glucose to gluconic acid and hydrogen peroxide. This first reaction step involves the cofactor flavin adenine dinucleotide (FAD) as first electron acceptor that is thereby reduced to FADH2. Molecular oxygen O2 then reacts with FADH2 to yield back FAD and the final product hydrogen peroxide H2O2. Oxygen consumption is measured by polarographic methods (not used in clinical chemistry) or the production of hydrogen peroxide is detected by electrochemical or chromogenic methods. The different chromogens (C) used (e.g., o-dianisidine, p-aminophenazone/phenol) act as hydrogen donors (Cred), which are oxidised (Cox) by H2O2 from the glucose reaction, with the colour change being proportional to the glucose concentration. Modified Clark electrodes (Fig. 1) are being used without diluting the sample in the classical blood gas analysers, in the i-Stat (Abbott Laboratories, USA) and in different glucose analysers or after dilution of the blood sample in the YSI glucose analysers (Yellow Springs Instruments, Yellow Springs Ohio, USA). If ferrocene or hexacyanoferrate are being used as final electron acceptors, the modified Clark electrodes can be replaced by simple, inexpensive single-use electrodes (sensor strips).
Glucose-oxidase (GO):

\[
\text{Glucose} + H_2O + O_2 \xrightarrow{GO/FAD} \text{Gluconic acid} + H_2O_2
\]

**Chromogenic methods** (colour change from oxidation of dyes is measured):

\[
H_2O_2 + C_{\text{red}} \xrightarrow{\text{Peroxidase}} H_2O + C_{\text{OX}}
\]

**Clark electrode and modifications** (current generated is measured):

platinum anode \( H_2O_2 \rightarrow 2H^+ + O_2 + 2e^- \)

silver cathode \( 4H^+ + O_2 + 4e^- \rightarrow 2H_2O \)

**Sensor** (current generated is measured):

\[
\text{Glucose} + \text{GO} - \text{FAD} \rightarrow \text{Gluconolactone} + \text{GO} - \text{FADH}_2
\]

\[
\text{GO} - \text{FADH}_2 + 2\text{Fe}^{3+} \rightarrow \text{GO} - \text{FAD} + 2\text{Fe}^{2+} + 2\text{H}^+
\]

\[
2\text{Fe}^{2+} \rightarrow 2\text{Fe}^{3+} + 2e^-
\]

The glucose oxidase reaction itself is highly specific, yet several reducing substances (e.g., ascorbic acid and acetaminophen) can interfere with the indicator redox reaction. The most significant problem for GO-based instruments is the dependency on the oxygen content of blood samples. Because of the different variations of GO systems, there can be anything from almost none up to very strong oxygen interference: in the cases of oxygen being the last electron acceptor (e.g., blood gas analysers and YSI), there is no interference as long as there is enough oxygen to run the reaction. On the other hand, GO systems using mediators (e.g., ferrocene) instead of oxygen can sometimes encounter strong interferences in case of higher blood oxygen concentration (see influences). This is because oxygen itself competes with the mediator as electron acceptor, thereby causing possible false low glucose concentrations.

![Modified clark electrodes](image)
Glucose dehydrogenase (GDH) requires the cofactor NAD, pyrroloquinolin-chinone (PQQ) or FAD as first electron. The resulting NADH could be measured directly or used for a chromogenic reaction (HemoCue). Again, in case of FAD (Ascensia contour, Bayer) and PQQ (Accu-Check inform, Roche), the use of mediators allow the use of sensor strips.

Glucosedehydrogenase (GDH):

\[
\text{Glucose} + \text{NAD}^+ \xrightarrow{\text{GDH}} \text{Gluconolactone} + \text{NADH (Absorbance measured)}
\]

Chromogenic methods (colour change of dyes is measured)

\[
\text{NADH} + \text{MTT} \xrightarrow{\text{Diaphorase}} \text{Formazan} + \text{NAD}
\]

MTT : \(3 - (4', 5' - \text{dimethylthiazol}) - 2 - \text{yl}) - 2, 4 - \text{diphenyltetrazoliumbromid}

Sensor (current generated is measured):

\[
\text{Glucose} + \text{GDH} - \text{PQQ} \rightarrow \text{Gluconolactone} + \text{GDH} - \text{PQQH}_2
\]

\[
\text{GDH} - \text{PQQH}_2 + 2\text{Fe}^{3+} \rightarrow \text{GDH} - \text{PQQ} + 2\text{Fe}^{2+} + 2\text{H}^+
\]

\[
2\text{Fe}^{2+} \rightarrow 2\text{Fe}^{3+} + 2e^-
\]

Being less specific than glucose oxidase or the combination of hexokinase/glucose-6-phosphate dehydrogenase, GDH also reacts with mannose, maltose, xylose, glucosamine and 2-desoxyglucose. Systems using GDH-based methods are, in general, less prone to interferences from exogenous substances and blood oxygen content.

Hexokinase (Hk) turns glucose into glucose-6-phosphate and also reacts, for example, with fructose, mannose and glucosamine. It is only the second step that yields the necessary specificity for glucose by using glucose-6-phosphate dehydrogenase to oxidise the intermediate to the final product, gluconate-6-phosphate. In addition to the two enzymes, the complete reaction requires ATP and NADP\(^+\). This method has so far only been used in central laboratory analyzers and not in POCT devices.

Hexokinase method (Hk):

\[
\text{Glucose} + \text{ATP}^{\text{HK}} \rightarrow \text{Glucose} - 6 - \text{P} + \text{ADP}
\]

\[
\text{Glucose} - 6 - \text{P} + \text{NADP}^+ \xrightarrow{\text{Glc-6-p-DH}} \text{Gluconat} - 6 - \text{P} + \text{NADPH} + \text{H}^+
\]

Instrument technology

Initially, in whole blood glucose measurements, paper strips have been used with the blood being wiped off at a prescribed time before the strip was introduced into the instrument (‘wipe technology’) and the colourimetric reaction was measured using a reflectance photometer. Meanwhile, this technique has thus changed that the colour change can be read from the opposite side of the strip (Fig. 2a) where the blood drop has been applied (‘non-wipe technology’). A strict prerequisite for this technique, however, is the separation of blood cells and lipids from the enzyme-impregnated reagent spot by a porous layer to prevent colour interferences from the whole blood spot itself. These layers actually can consist up to four individual pieces (Fig. 2) with specific properties such as being hydrophobic, hydrophil or porous and involve highly complex fabrication processes. It is important to be aware of the fact that in spite of whole blood being applied to the strip, the glucose concentration is measured in plasma or at least a ‘plasma-like’ fluid (no blood cells, none or fewer lipids). The HemoCue glucose analyser is a notable exception as the absorbance of the colourimetric
reaction is directly measured in lysed whole blood by a photometer (Fig. 2c). The move to electrochemical biosensors (Fig. 2b) not only caused a significant reduction of the amount of blood required for a reliable measurement, with no need for the blood sample to enter the meter at all, but also led to very short reaction times of a few seconds, built-in quality controls and the possibility to compensate for interferences using a third electrode. Most of the sensor test strips, however, still use the porous layer technique to separate the blood cells and lipids, thereby measuring glucose concentrations in plasma/plasma-like fluids. All electrochemical biosensors were based on amperometric detection methods when the FreeStyle (Abbott Diabetes Care) was introduced to the market as the first coulometric system. One of the major advantages is the comparable much weaker interference caused by the haematocrit of the blood sample (see influences and interferences). With a small area (electrode)/volume (blood) ratio, amperometric methods usually analyse only a small portion of the actual glucose content of the blood sample. The electrical current produced from the reaction is hereby directly proportional to the glucose concentration. In case of the coulometric method, there is a large area (electrode)/volume (blood) ratio and nearly the total amount of glucose present in the blood is measured with the charge being directly proportional to the glucose concentration. Besides interferences from endogenous and exogenous substances, haematocrit interference causes major problems when glucose POCT devices are being used in ICUs. There are many research and development activities in this area, and recently the Nova Stat Strip was introduced as a new system with gold electrodes and ‘multi-well’ technology. The four electrodes account for measuring glucose, interferences and haematocrit.

Even eight electrodes are now being used in the Accu-Chek Aviva strips: they are used for the control of reagents, test strip integrity, humidity, temperature, blood sample volume and haematocrit.

**Calibration**

In addition to the type of blood sample used, calibration of instruments is equally important and may often cause additional errors, and yet most of the time industry is not willing to tell the exact details of the calibration used. The reason for the calibration being so essential for POCT glucose devices lies within the nature of the instruments themselves. Whereas in routine clinical chemical analysers, in classical blood gas analysers and to some degree in the Hemocue analyser (adjustment of the photometer), calibration is done whenever necessary or at certain definite times during patient
measurements; in POCT, calibration of fabricated strips is final and cannot be changed. Most companies use a series of calibrations and the best fit is used for the actual charge of test strips (calibration code). Using gold electrodes in sensor strips (Nova Stat Glucose, Accu-Chek Aviva, see haematocrit) seem to stabilise the system with no need for additional calibration.

Depending on the glucose standard (aqueous or serum-based NIST SRM) and reference method used for calibration, the same instrument will give varying results, the most obvious being the calibration for whole blood and plasma. But just what is the reference method for glucose? There must be a reference method for each sample type as long as glucose concentration is being used, otherwise one has to cope with converting factors (see plasma equivalent). This might be right for most patients or statistically for groups of patients, but certainly not for each individual patient in the ICU with all the possible changes in haematocrit, oxygenation, perfusion and all the other interventions occurring (see assay principles and influences). Furthermore, the same POCT glucose device may even be calibrated differently depending on the country.

Specimen matrices: what are we actually measuring?

Although the measurement of glucose is one of the oldest established tests in the clinical chemistry laboratory, it is extremely complex and sometimes rather approximate due to the different types of the blood sample used. Glucose measurement can be performed in whole blood, plasma and serum, and these may be native, deproteinised or haemolysed (capillary whole blood). Although deproteinised plasma samples are no longer used in routine clinical laboratories, most of the original diagnosis criteria and decisions in diabetology were concluded from studies based on this sample type. The conversion made later for other types of blood samples was done not without problems, though.

The most important factor for the clinician to be aware of is the plasma/whole blood issue. Still somewhat difficult to understand, the difference between plasma and whole blood glucose values is basically due to the different content of lipids, proteins and cellular components. These different volumes (amounts) of solids dissolved in a given volume (blood sample volume) cause different volumes (amounts) of water to be present in this given volume (blood sample volume). Glucose is dissolved in – and solely – this aqueous part of the blood sample and not in the entire volume of the blood sample (which contains the above-mentioned dissolved solids such as proteins). This is the main reason for differing glucose concentrations in plasma and whole blood samples (Fig. 3). As there is a higher protein concentration (haemoglobin) in red blood cells compared to plasma (lower total concentration of albumin and other plasma proteins), the water content is lower in blood cells (mostly red blood cells) than that of an equal volume of plasma. Even with the ‘free’ glucose

![Figure 3](image.png)

**Figure 3.** Glucose concentration. Assuming a haematocrit of 0.43 and a water content for the cell fraction of 71% this fraction will make up of 31% (71% of 43%) of total water volume (whole blood). From the 57% plasma volume 93% will be water thus giving a water content of 53% for the plasma portion of whole blood. The total water content of whole blood then is 84% (53% + 31%). For a haematocrit of 0.43 the plasma/whole blood ratio of water content is 0.93/0.84 = 1.11, which reflects the 11% higher glucose values in plasma compared to whole blood.
concentration (activity) being the same in plasma water and red blood cell water (mmol glucose per kg water) the concentration of glucose per unit volume of red blood cells (mmol glucose per litre red blood cells) is lower than that per unit volume of plasma (mmol glucose per litre plasma). The concentration of glucose per unit volume of whole blood is in between that for plasma and red blood cells. As the water content of whole blood is the sum of plasma water and red blood cells water, glucose concentration will strongly depend on the haematocrit of the sample (Fig. 3). Although this volume displacement effect caused by proteins had been known since the late 1920s, little attention had been paid to this effect in blood serum by clinical laboratories until Bürgi et al. published a first mathematical calculation.

Assuming a haematocrit of 0.43 and water content for the cell fraction of about 71% (0.71 kg water per litre), this fraction will make up for 31% (71% of 43%) of the total water volume (whole blood). From the 57% plasma volume, 93% will be water (0.93 kg water per litre), thus giving a water content of 53% for the plasma portion of whole blood. The total water content of whole blood then is 84% (53% + 31%). For a haematocrit of 0.43 the plasma/whole blood ratio of water content is 0.93/0.84 = 1.11, which reflects the approximately 11% higher glucose values in plasma compared to whole blood. With no changes in the protein concentration of plasma or red blood cells, a change in haematocrit from 0.43 to 0.65 (newborns) will change the plasma/whole blood ratio for glucose from 1.10 to 1.18. If diluted whole blood samples are being used (e.g., YSI glucose analyser), there will be an additional dilution error dependent on the dilution factor. For a 1:24 dilution of whole blood (haematocrit of 0.43), this would actually be a 0.84:24 dilution of the water content and cause an additional error of about 19% between diluted and undiluted sample. The type of blood sample used is an important factor in interpreting the blood glucose values and has to be considered as well as the instrument technology of the blood glucose device.

Furthermore, blood may be arterial, capillary or venous in origin and, in case of continuous glucose monitoring, even interstitial fluid is being used instead of blood. Although the differences between capillary and arterial and between venous and arterial blood glucose concentrations are noted as being 5 mg dl\(^{-1}\) and 10 mg dl\(^{-1}\), respectively, this is only a rough estimation and might only be true for a healthy person not being in the postprandial state. Otherwise, this correlation is strongly dependent on tissue perfusion, blood oxygenation and pH, temperature, nutritional state and glucose consumption (see influences and interferences).

### Plasma equivalent

In 1990, Fogh-Anderson et al. already reported on the discrepancy between glucose concentration in whole blood and plasma when measured by classical methods. Even though they recommended direct-reading glucose sensors, they were aware of the problems using activity and molality instead of concentration and molarity in daily clinical routine. A possible solution to this problem had been seen in converting activity (molality) into concentration (molarity) by means of a mathematical calculation (see specimen matrices). Based on this idea in 1998, a proposal for standardising direct-reading biosensors for blood glucose was published. Instead of correcting individual whole blood samples, the authors proposed to use serum-based glucose certified standard reference material (NIST SRM 965, National Institute for Standards and Technology) for calibration. This would result in whole blood samples to be reported as plasma-equivalent values (see calibration). Finally, in 2005, the International Federation of Clinical Chemistry (IFCC) published its recommendation on reporting glucose measurements as plasma values independent of the nature of the samples. At the same time, the conversion factor of 1.11 (see specimen matrices) was defined for the plasma–whole blood conversion. Of course, a very important consequence of this is not to use plasma as blood type sample for plasma-correlated POCT devices. It will be interesting to see if these plasma-correlated glucose devices will just be used in the glucose self-testing community of diabetic patients or will actually be applied in POCT in hospitals and even in ICUs despite all the influences and interferences described earlier (see influences and interferences). Even with these plasma-correlated glucose devices, one has to keep in mind that glucose concentrations will always stay haematocrit (and protein in general) dependent regardless of the calibration.
Influences and Interferences of glucose measurements

Multiple variables affecting glucose measurements arise from factors due to the glucose device methodology itself and the instrumentation techniques involved (interferences) as well as from factors that lie within the patients themselves (influences). Especially in ICU patients, many of these variables may be present at the same time. All these influences and interferences have to be tested individually and for every single glucose device rather than for a specific methodology (e.g., GO-based instruments) as even within the same ‘basic’ methodology influences and interferences may differ significantly (see assay principles and POCT evaluation).

Haematocrit is one of the most important factors influencing POCT glucose measurements. Due to the volume displacement effect caused by proteins (see specimen matrices), there always must be a difference between plasma and whole blood glucose values as long as concentrations rather than activities are being measured and may account for up to 30%. In addition, still most blood glucose strips retain red blood cells through a filtering process and measure glucose content in plasma/plasma-like fluids in their reaction zone. Whole blood samples with differing amounts of red blood cells will alter flow and volume of plasma entering the reaction zone and thereby influencing the results. Even the YSI Blood Glucose Analyser (Yellow Springs Instruments USA), which is often used as reference method in POCT evaluation studies, yields glucose results dependent on haematocrit when whole blood samples are used. In general, an increase in haematocrit will cause a decrease in glucose measurement and vice versa. The least influence in the past had been reported for the HemoCue glucose analyser, which can be explained by the fact that it uses lysed whole blood. Using four electrodes for measuring glucose, interferences and haematocrit, the Nova Stat Glucose does not show any significant error. Similar results should be obtained for the Accu-Chek Aviva strips with its eight electrodes, including one for the control of haematocrit. In theory, the only systems that should not be affected by haematocrit are instruments using direct-reading electrodes without sample dilution as those being used in blood gas analysis.

Blood oxygenation is another patient factor that could cause false glucose readings (see assay principles). Whereas classical (modified Clark) electrodes require a minimum of oxygen for the electrochemical reaction (blood gas analyser, YSI), high oxygen tension could cause false low glucose measurements in instruments with a mediator (e.g., ferrocene) as final electron acceptor. In these cases, oxygen competes directly with the mediator for the oxidation of FADH2. Although this influence is independent from the blood-sampling site, it will be greatest in case of arterial blood due to its natural higher oxygen tension. Glucose measurements in surgical ICU patients will always tend to have greater problems as they are prone to more and sometimes more dramatic changes in haematocrit and oxygenation (e.g., cardiosurgery).

Yet another rather complex influence is hypotension of the patients in ICUs. Hypotension itself may cause a reduction of perfusion and thereby increase glucose utilisation that finally will result in a significant increase of the difference between capillary whole blood and venous plasma glucose measurements. This actually involves two opposing effects (see specimen matrices). Capillary glucose values are higher than the corresponding venous values (arterio-venous difference), yet the whole blood glucose measurements (capillary samples) are lower than their corresponding plasma values (venous samples). Comparing capillary whole blood glucose measurements to venous plasma values, both blood samples can actually show the same value and, in case of plasma-correlated capillary whole blood instruments, this could even lead to higher values compared to the venous plasma values. These effects might even be worsened during parenteral feeding and are completely independent of the glucose instrument used.

Influences like blood pH or body temperature are theoretically existent but clinical significance has not been unequivocally proven so far. Influences arising from bilirubin, triglycerides or para-proteins have been reported less frequently.

Most interferences known from drugs or endogenous metabolites (e.g., vitamin C, acetaminophen, salicylate, catecholamines, ibuprofene, uric acid and bilirubin) have been reported for GO-based devices with the second reaction step being mostly involved. GD-based devices show almost no
interferences at all and then directly in the first step of reactions (see assay principle). In addition to these more general influences, there are a few device-specific interferences. In case of the HemoCue system, these are the interferences caused by methaemoglobin > 10% or intralipid. Yet another very interesting issue is the icodextrin/maltose interference of GD-based devices. This issue again demonstrated clearly the importance of knowing not only the basic chemistry of glucose reactions but also all its side reactions within a given specific device. On 4 November 2005, there had been a Food and Drug Administration (FDA) warning on falsely high glucose values measured using GD-based glucose devices in patients with elevated plasma level of maltose, galactose or xylose that had to be corrected within 5 days. Whereas the original warning included all GD-based instruments, it then had to be restricted only to devices using pyrroloquinoline quinine as a cofactor (GDH-PQQ). Other GDH-based devices using GDH-NAD (HemoCue) or GDH-FAD (Ascensia contour) did not show this interference and could be used as well as all GO- or hexokinase-based devices. Most commonly, this problem may be encountered in peritoneal dialysis with Icodextrine (e.g., Extrarenal Baxter) being metabolised to maltose within the human body. Problems with maltose directly or galactose or xylose are much less frequent.

In addition to these patient factors and interferences, the operator must be seen as the probably largest source of error. Quality management of POC Glucose testing, especially in an ICU, needs continuous education and training, connectivity for the devices used, built-in quality controls within the devices and there must be enough time provided for the persons measuring glucose in order to do it properly.

Evaluation of POCT glucose devices

Although in the two basic studies of van den Berghe et al. different glucose analysers (ABL 700 Radiometer, Denmark; HemoCue B glucose analyser, Sweden) with different sample matrices (arterial and capillary whole blood) were used, the same reference values were applied for both the targets of TGC (80–110 mg dl⁻¹) and the definition of hypoglycaemic events (<40 mg dl⁻¹). The problems of POCT glucose measurements and the question of the right choice of devices and blood samples soon became evident and were addressed. Scott et al. even speculated the POCT glucose devices being used as a possible source of failure or success of tight glycaemic control by stating that the original van den Berghe et al. study with a 34% decrease in hospital mortality used arterial blood samples and a precise arterial blood gas instrument for glucose measurement, whereas many of the studies that failed to show improved mortality for medical ICU patients used POCT glucose meters with even capillary blood samples at times. Unfortunately, the methods used to measure glucose are frequently not described in studies of tight glycaemic control: in examining the original articles included in the meta-analysis by Wiener et al., Scott et al. found that the glucose method was described in only 10 of the 27 studies.

In recent years, the number of publications in journals from the field of intensive care medicine and related areas on POCT glucose measurements and method of evaluations have increased significantly. In these, different central laboratory methods based on different assay principles (e.g., YSI Glucose Analyzer, Dimension RXL, Glucose Analyzer Beckman Coulter and Hitachi 747 Analyzer) were declared ‘reference methods’, the time needed between drawing blood and the actual measurement in the central laboratory was neither standardised nor reported, and different sampling sites with different blood samples were used. Regarding these ‘reference methods’ used in the central laboratories, one must consider that even with the use of glycolytic inhibitors (e.g., NaF), there will be a drop in glucose concentration of up to 6% or 10 mg dl⁻¹ within the first hour after the blood draw. However, all these pitfalls in POCT method evaluation are not only present in the field of intensive care and related areas but are also found in almost all published studies. Some studies reported poor results and concluded that data from glucose monitors are unreliable and unsatisfactory. Others have reported positive results with even the same POCT device and stated that data from POCT glucose devices are accurate and meet performance expectations. Mahoney et al. investigated 52 recently published evaluations of POCT glucose devices regarding the compliance with recommendations or quality guidelines for conducting and reporting glucose monitor evaluation studies. These guidelines included
20 recommendations from the Standards for Reporting Diagnostic Accuracy (STARD) and 18 recommendations from the Clinical and Laboratory Standards Institute (CLSI). Not a single study fulfilled all the requirements and the median was only 53% of the specifications. Mahoney et al. concluded that the inconsistency of results from POCT glucose evaluation studies in the literature is problematic as it causes confusion and may slow down adoption of new indications for glucose monitors (e.g., continuous glucose monitoring).

POCT glucose devices should be evaluated prior to their use for TGC in ICU. Due to lack of standard reference material for whole blood glucose, human whole blood has to be used for these studies and a protocol that is strictly adhered to. Although there are several guidelines available, investigators have neither used nor adopted a standardised, generally accepted approach. Potential sources of error in the evaluation of POCT glucose devices to be considered are analytical imprecision, analytical bias, protocol-specific bias and patient interferences. Bias and imprecision are controlled by testing products that conform to specifications, protocol-specific bias by adherence to careful study design and random patient interferences by inclusion and exclusion criteria for recruitment of study participants. Recently, Mahoney et al. proposed a standardised 14-step checklist that facilitates the incorporation of 10 international consensus standards, quality guidelines and acceptance criteria into the design and reporting of POCT glucose device evaluation protocols. This checklist outlines a standardised approach to POCT glucose device evaluations based on international standards and consensus recommendations that is evidence-based, scientifically defensible and sufficiently descriptive.

Using TGC protocols, clinicians need rapid, easy-to-use POCT glucose devices with high-quality ‘laboratory-equivalent’ results. Acceptable deviation for POCT glucose results from the reference value is still under discussion and a total error of 5% had been proposed. Interestingly, this goal is even stricter than most of the national recommendations for laboratory instruments. As treatment decisions in TGC protocols depend heavily on the patient glucose values, the future use of POCT glucose devices must be standardised. Insufficient quality of POCT glucose devices could be the source of mixed and conflicting outcomes of TGC studies and may even be harmful to patients. The checklist proposed by Mahoney et al. could serve to develop protocols for POCT glucose device evaluation and help choose the right instruments.

Continuous glucose monitoring (CGM)

TGC in critically ill patients requires frequent blood sampling for glucose measurements with correct and strict adherence to a usually rather complex insulin infusion protocol. Despite continuous education and staff monitoring, the protocol therefore might be too difficult to always be precisely followed by a busy ICU staff. As these protocols are usually based upon discrete glucose measurements, thereby possibly missing fast glucose changes, continuous glucose monitoring might be a promising alternative that could be beneficial for maintaining target blood glucose levels and avoiding hypoglycaemia at the same time. Beginning in the mid-1960s, further development finally resulted in the first FDA-approved, commercial, continuous glucose monitoring (CGM) system in 1999. Recently, there have been several reviews of CGM and discussions about different approaches for the assessment of CGM systems. There are several subcutaneous CGM systems and one intravenous CGM system in use. Because of the varying conditions in the interstitial fluid compartment, calibration of the sensor signal must be performed by means of conventional (capillary) blood glucose measurements to transform the sensor signals from subcutaneous CGM systems into ‘blood’ glucose values. However, the relationship between changes in blood glucose and in ISF glucose is rather complex and can be affected by tissue perfusion, temperature and local humoral factors. The continuous intravenous blood glucose monitoring device, originally used as artificial endocrine pancreas, has a closed-loop glycaemic control system maintaining blood glucose levels through automatic insulin and glucose infusions. Continuous glucose monitoring might therefore be a promising alternative for maintaining TGC; however, it still needs further evaluation of its accuracy and reliability together with its clinical utility in critically ill patients.
Practice points

Glucose analysis is based on either chromogenic or electrochemical reactions of the three enzymes, glucose oxidase, glucose dehydrogenase or hexokinase/glucose-6-phosphate dehydrogenase. This gives rise to method-specific interferences such as the blood oxygen tension dependency of glucose oxidase or interfering substances and drugs, which are major issues in ICU patients.

Multiple variables affecting glucose measurements arise from the patients themselves and especially in ICU patients may be present all at the same time, for example, hypotension, abnormal haematocrit or acid–base abnormalities.

The most important factor for the clinician to be aware of is the difference between plasma and whole blood glucose values, basically due to the different content of lipids, proteins and cellular components in the different blood samples used. Besides these matrix effects, the sampling site together with the nutritional status of the patient has to be taken in consideration when comparing blood glucose values.

All these influences and interferences have to be tested individually and for every single glucose device rather than for a specific methodology as even within the same ‘basic’ methodology influences and interferences may differ significantly. In the evaluation of any analytical device, standardised protocols have to be used, analytical imprecision and bias, protocol-specific bias and patient interferences have to be considered. Care has to be taken to choose the suitable reference method, which may not be the one available in the central laboratory where the study is being performed.

Future research

As treatment decisions in tight glycaemic control depend heavily on the patient glucose values, clinicians need rapid, easy-to-use POCT glucose devices with ‘laboratory-equivalent’ results. The future use of these POCT glucose devices must be standardised and interferences and influences must be kept at a minimum.

Continuous glucose monitoring (CGM) might be an alternative to the frequent blood sampling required for POCT glucose measurements. Especially continuous intravenous blood glucose monitoring devices with a closed-loop glycaemic control system could be very beneficial for maintaining target blood glucose levels and avoiding hypoglycaemia at the same time. However, CGM still needs further evaluation of its accuracy and reliability together with its clinical utility in critically ill patients before it can find its way into clinical practice.

Several recommendations and guidelines for glucose monitoring evaluation studies have been published, but so far, there is no consensus on generally accepted assessment criteria. Future studies should be carefully designed and follow guidelines for methodological and reporting quality that are evidence-based, scientifically defensible and sufficiently descriptive to allow for test and result reproducibility. By using a checklist that combines key elements from different consensus recommendations, the quality of glucose monitor evaluation studies could be improved.

References


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