Review Article

Accuracy and reliability in glycemia monitoring in adult critically ill patients: an integrative review

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ABSTRACT

Reliable glycemia monitoring in critically ill patients is essential to safe care. Biases in measurements may result in imprecise values, causing healthcare teams to interpret results mistakenly and change therapeutic conducts toward improper directions. The aim of the present study was to search for the scientific production about factors related to accuracy and reliability of glycemia monitoring in patients admitted to intensive care units by consulting the CINAHL, PubMed, Web of Science, Scopus and Virtual Health Library databases. Evidence from 18 papers that addressed accuracy and reliability in glycemia monitoring revealed aspects such as measurement method, sample type, characteristics of critically patients and equipment handling. Healthcare teams should consider the advantages and drawbacks of each method, taking into account their care realities and patient safety.

Descriptors: Blood Glucose; Data Accuracy; Critical Care; Intensive Care Units; Point-of- Care Testing.

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INTRODUCTION

Changes in glycemic levels are common in critically ill patients. Inflammatory responses, the stress caused by the body reaction to the disease and treatments can provoke insulin resistance, glucose intolerance, and hyperglycemia[1-2]. The latter is considered a severity marker, strongly associated with the increase in risk of death[3-5], because it causes imbalances in the immune system and in the inflammatory response, which becomes unspecific. As a consequence, patients develop oxidative stress, mitochondrial dysfunction, cell death and tissue injury, with posterior organ failure[6-9].

The literature in the field includes investigations carried out in intensive care services where there was an attempt to keep glycemia levels as stable as possible, which decreased death rates significantly[3,10-14]. It is important to emphasize that stabilizing glycemia concentration demands interventions such as insulin administration via continuous infusion, which can increase the risk of hypoglycemia, a condition that may be more harmful than hyperglycemia[3,10-15].

Given this scenario, glycemia monitoring in intensive care units (ICUs) is a common care procedure which takes place through glycemia measurements to adjust insulin or glucose administration[13,16].

Currently, glycemic control in ICUs is achieved through the use of continuous[17-18] (for instance subcutaneous or intravenous sensors) and intermittent[16,19-20] (such as glucose meters, hemogasometers and lab tests) monitoring devices. Mobile glucose meters are commonly used to assess glycemia levels, because of their convenience, low cost and easy handling[21]. In addition to these characteristics, glycemia measurements with this apparatus and proper strips allow the application of the method in arterial, venous or capillary blood[21-22], and can be performed frequently, depending on patients' clinical needs and concentrations obtained in previous measurements. The latter advantage is useful for allowing immediate therapeutic interventions and decreasing the chances of complications resulting from a metabolic imbalance.

Accurate and reliable glycemia monitoring can be crucial to the outcome of patients' clinical condition and safe care. It is believed that inaccurate or unreliable results lead healthcare teams to interpret exams mistakenly and change therapeutic conducts[22-23]. Accurate measurements guide insulin and glucose prescriptions and help in nutritional therapy[24-25], facilitating recovery from the physiological stress that derives from critical treatment.

From this perspective, it is considered that reducing the oscillation of glycemia levels and determining a glycemia variation range that can be safe for critically ill patients is as important as obtaining reliable glycemia outputs. The objective of the present study was to scrutinize scientific literature to find the production about factors related to accuracy and reliability in glycemia monitoring in critically ill patients from ICUs.

METHODS

The present investigation is an integrative literature review focused on gathering and summarizing evidence reported in original scientific papers about the subject. The study was carried out in six steps: definition of the problem and objective of the review or theme identification, establishment of inclusion and exclusion criteria for the material and literature search, classification of primary studies and definition of the information to be extracted from selected publications, analysis of the papers included in the sample, results interpretation and summarization of the knowledge disseminated by the studies[26-27].

The PICO strategy was applied to formulate the guiding question of the review. The acronym PICO stands for patient, intervention, comparison and outcomes and aims to find the best available evidence in the search in each database[28]. In the present investigation, the letters in the acronym refer to: P - critically ill patients from ICUs, I – glycemia monitoring, C – does not apply and O – accuracy and reliability.

The guiding question was: "What is the evidence available in the literature on factors related to accuracy and reliability in glycemia monitoring in critically ill patients from ICUs?" The databases used to search for papers were the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, Web of Science, Scopus and the Virtual Health Library (or BVS, as per its acronym in Portuguese). The controlled descriptors were "critical care", "point-of-care testing", "blood glucose" and "data accuracy". These descriptors were defined by consulting the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) websites with the Boolean operator "AND". It is noteworthy that tests including keywords such as "reliability" and "feasibility" combined to the mentioned descriptors were performed, in the same databases and library. However, the publications found with these combinations of expressions had already been found in the search with descriptors only.

The eligibility criterion was full primary studies addressing accuracy and reliability in glycemia monitoring in critically ill patients from ICUs published in English, Spanish and Portuguese from January 2006 to December 2016. This period was defined to restrict the analysis to more recent publications. Studies whose samples were made up exclusively of newborn, pediatric, diabetic, burned, cardio-surgical or neuro-surgical patients were not included in the review because of the specificities of these conditions.

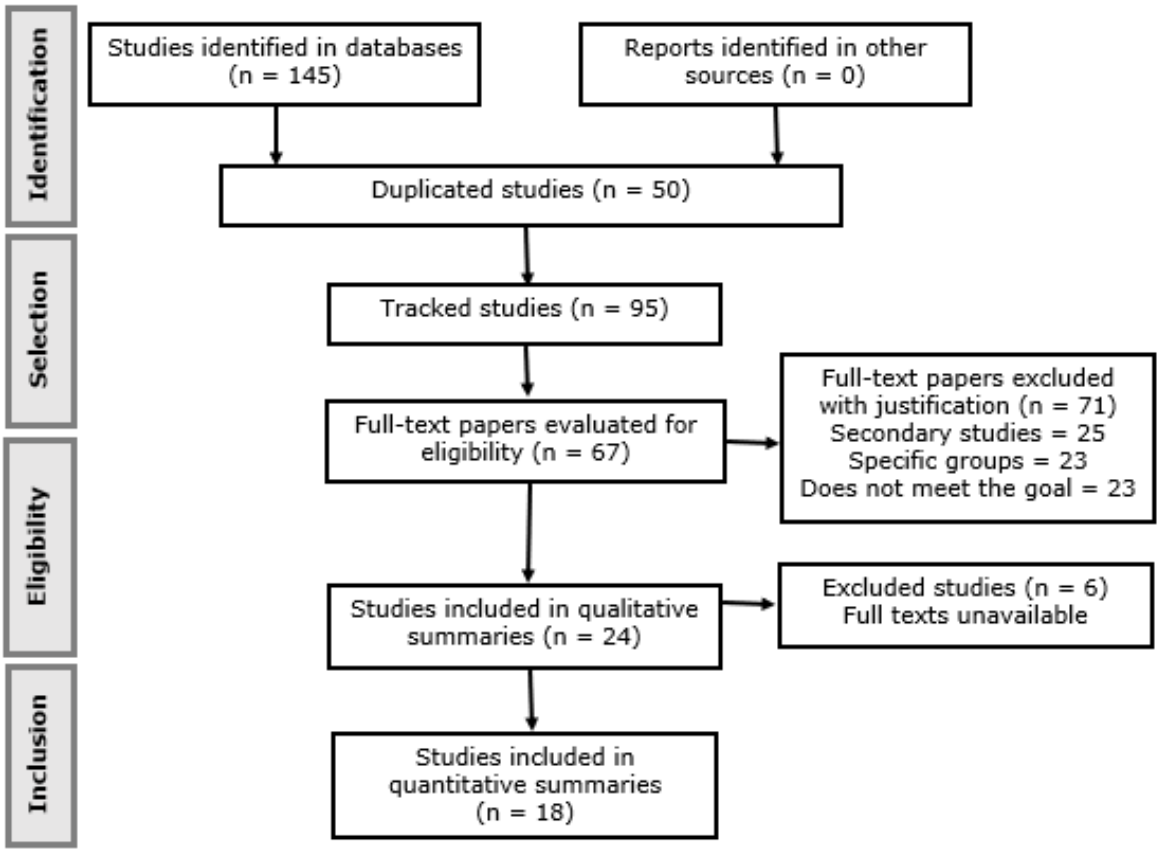
A validated instrument that includes paper identification, authors, publication type, methodological and intervention details, studied interventions, results and recommendations or conclusions was used to extract data from selected papers[29].

The word "accuracy" means the capacity to determine the exact value, expressed as the difference between the average of measured values and the exact value or, in the present review, the glucose concentration assessed by a reference method[30-31]. Reliability refers to a test's capacity to reproduce the same results when repeated or to produce data which agree with the outcomes of methods with the same purpose, and it is expressed by the distribution of individual measurements around a mean value[30]. Correlation and regression analyses, the Bland-Altman plot and the Clarke error grid approach are some of the metrics used to examine accuracy and reliability in studies[21].

The selected papers were classified according to the methodological design and evidence level, and data summary is presented descriptively.

Evidence levels were categorized hierarchically according to the adopted methodological approach. Level I encompassed systematic reviews or metanalysis of relevant randomized controlled clinical trials (RCCTs) or clinical guidelines based on systematic reviews of RCCTs. Level II covered evidence obtained in properly designed RCCTs. Evidence reported on properly designed clinical trials without randomization was grouped in level III. Level IV was reserved for evidence resulting from case-control or cohort studies with proper design. The content described in systematic reviews of qualitative and descriptive studies was included in level V. Level VI enclosed evidence originated from a single descriptive or qualitative study. Opinions of authorities and/or specialist committee reports constituted level VII[32].

Figure 1: Paper selection process for inclusion in the integrative review.



Source: Flowchart designed by the authors according to the recommendations by Moher et al. (2015)[33].

RESULTS

The review sample had 18 papers. The analysis of the publications included in this study highlighted data about accuracy and reliability in glycemia monitoring in samples including critically ill patients. Chart 1 exhibits the characteristics of the material selected for review.

Chart 1. Papers included in the integrative review according to author, year of publication, country of origin, evidence level, sample, experimental design, methods and main results.

Author, year, country of origin, evidence level	Sample, age	Study design, glycemia measurement methods	Main results
Pereira et al., 2015[34], Brazil, IV.	145 patients with an average age of 60.9 years	Prospective and cross-sectional. **Devices used:** Precision PCx (Abbott, Illinois, USA) and Accu-chek Advantage II glucometer (Roche, Basel, Switzerland). **Reference method:** Lab test. **Blood sample type:** Arterial (permanent catheter), capillary and venous (central catheter).	**Accuracy and reliability:** The two tested glucose meters presented low accuracy and precision, especially for venous blood from central venous catheters. There was a variation between the results obtained with the different methods. **Patient-related factors:** Reduction of hematocrit level and acidosis were associated with differences between glycemia measurements with arterial and venous blood. The use of vasopressors increased the error in measurements with capillary blood.
Van Hooijdonk et al., 2015[35], Netherlands, IV.	50 patients with average age of 65 years, 105 sensors, 929 samples.	Prospective. **Devices used:** Subcutaneous continuous glycemia monitoring system Medtronic MiniMed (Medtronic Inc., Northridge, CA, USA). **Reference method:** RapidLab 1265 blood gas analyzer (Siemens Healthcare Diagnostics, The Hague, Netherlands). **Blood sample type:** Arterial.	**Accuracy and reliability:** The subcutaneous continuous sensor did not meet ISO 15197:2003 standards. **Patient-related factors:** The device was more precise in diabetic patients. **Equipment handling-related factors:** The increase in the number of calibrations augmented the precision of the apparatus.
Garingarao et al., 2014[36], Philippines, IV.	180 patients, of whom 89 were normotensive (average age of 51.3 years) and 91 were hypotensive (average age of 54.7 years), 186 measurements.	Prospective and cross-sectional. **Devices used:** Accu-Chek Active Meter glucose meter (Roche Diagnostics, Indianapolis, Indiana, USA). **Reference method:** Lab test. **Blood sample type:** Venous from peripheral veins or from central and capillary catheters.	**Accuracy and reliability:** In the normotensive group, the outputs of the glucose meter agreed with the reference test. In the hypotensive group, the agreement was 79%, thus failing to comply with ISO 15197:2003 guidelines. **Patient-related factors:** High heart and respiratory rate, lower Glasgow scale scores, need for mechanical ventilation with lactic acidosis and reduction in leukocyte count can be associated with the poorer performance of the glucose meter in the hypotensive group.
Lonjaret et al., 2012[37], France, IV.	75 patients with an average age of 59 years, 304 measurements.	Prospective and observational. **Devices used:** CONTOUR® TS glucose meter. (Bayer HealthCare, Tarrytown, NY, USA). **Reference method:** Lab test. **Blood sample type:** Capillary and arterial.	**Accuracy and reliability:** Arterial samples led to more precise results than capillary samples. The outputs of the glucose meter did not meet ISO 15971:2003 criteria. The glucose concentrations in capillary blood were underestimated. **Patient-related factors:** Lactate levels and use of vasoactive drugs and insulin decrease the precision of measurements regardless of the blood sample type.

Author, year, country of origin, evidence level	Sample, age	Study design, glycemia measurement methods	Main results
Juneja et al., 2011[38], India, IV.	200 patients: 100 in the study group (hypotensive people with septic shock who used vasopressors, with an average age of 63 years) and 100 in the control group (normotensive people with an average age of 63.9 years).	Prospective and case-control. **Devices used:** One Touch Ultra blood glucose monitoring system (LifeScan, Johnson & Johnson). **Reference method:** Not mentioned. **Blood sample type:** Capillary and arterial.	**Accuracy and reliability:** The results of the measurements with arterial and capillary blood were not reliable in the hypotensive group. The precision of the device was not in accordance with ISO 15197:2003 criteria. The outputs in the control group were reliable. **Patient-related factors:** Hypotension and use of vasopressor reduce the precision of the equipment used.
Fekih Hassen et al., 2010[39], Tunisia, IV.	43 hyperglycemic patients grouped in two sets: group 1, with 23 hemodynamically stable patients with an average age of 57 years, and group 2, with 20 patients who used catecholamines, with an average age of 64 years.	Prospective. **Devices used:** Accu-Chek (Roche Diagnostics, Mannheim, Germany). **Reference method:** Lab test. **Blood sample type:** Capillary (from the digital pulp and the ear) and venous.	**Accuracy and reliability:** The measurements performed with the device were not precise for group 2, whose patients used a vasopressor drug, regardless of the collection place. Sampling blood from the ear did not improve the precision of the glycemia result. **Patient-related factors:** Use of catecholamines reduces the accuracy of the glucose meter.
Karon et al., 2009[40], United States, IV.	50 patients, age not informed.	Prospective. **Devices used:** Accu-Chek Inform (Roche Diagnostics, Indianapolis, IN) and Stat-Strip (Nova Biomedical, Waltham, MA). **Reference method:** Lab test. **Blood sample type:** Venous, from center venous catheter, peripherally inserted central catheter or peripheral puncture.	**Accuracy and reliability:** The Accu-Chek Inform glucose meter exhibited differences of up to 20 mg/dL in comparison with lab tests. Stat-Strip showed overestimated values, mainly in center venous catheter blood samples.
Hoedemarekers et al., 2008[41], United States, IV.	Three groups: - 85 critically ill patients (197 samples); - 53 critically ill patients (82 samples); - 47 noncritically ill patients (74 samples). Average age of 55 years.	Prospective and observational. **Devices used:** Accu-Chek Sensor (Roche Diagnostics, Abbott Park, IL), Precision (Abbott Diagnostics) and HemoCue, Sweden. **Reference method:** Lab test. **Blood sample type:** Arterial.	**Accuracy and reliability:** The glycemia results displayed by the three devices did not meet ISO criteria. **Patient-related factors:** Patients with a higher score in severity and prognostic scales had more imprecise outputs, which were overestimated and consequently induced the unnecessary administration of insulin.

Author, year, country of origin, evidence level	Sample, age	Study design, glycemia measurement methods	Main results
Price et al., 2008[42], United Kingdom, IV.	17 adult patients and 1,101 measurements, divided according to the following comparison pairs: continuous glucose monitoring system with glucose meter and glucose meter with different blood samples. The average age varied according to the diagnosis group.	Retrospective. **Devices used:** Guardian continuous glucose monitoring system (CGMS Gold, Medtronic MiniMed, Northridge Calif, USA) and Accu-Chek Advantage glucose meter, F. Hoffman-La Roche, Basel, Switzerland). **Reference method:** Accu-Chek Advantage glucose meter. **Blood sample type:** Capillary and arterial.	**Accuracy and reliability:** The results of the continuous glucose monitoring system were closer to those of the glucose meter for arterial blood samples, and the former overestimated the concentration. The results of the glucose meter were not reliable regardless of the blood sample type.
Critchell et al., 2007[43], United States, IV.	80 patients with an average age of 58.8 years, 77 samples.	Prospective and observational. **Devices used:** Accu-Check Inform glucose meter (Roche Diagnostics, Mannheim, Germany). **Reference method:** Lab test. **Blood sample type:** Capillary and venous.	**Accuracy and reliability:** The concentrations displayed by the glucose meter were overestimated and 19% of the outputs were not in agreement with ISO criteria. The device was more precise with capillary blood samples. **Patient-related factors:** Hematocrit level, edema and use of vasopressors can influence the precision of measurements with capillary blood in critically ill patients.
Lacara et al., 2007[44], United States, IV.	49 patients with an average age of 66.8 years.	Prospective. **Devices used:** SureStep Pro Hospital Meter and SureStep Pro Hospital Products Test Strips (Johnson & Johnson, Milpitas, California). **Reference method:** Lab test. **Blood sample type:** Arterial and from peripheral venous catheter; capillary for the glucose meter test.	**Accuracy and reliability:** The accuracy and reliability of the glucose meter were higher with capillary blood in comparison with those observed for the other samples. **Patient-related factors:** Low hematocrit and carbon dioxide levels reduced the reliability of the glucose meter. The device displayed overestimated glucose concentrations with arterial blood samples. The average blood pressure did not influence the outputs.
Corstjens et al., 2006[45], United States, IV.	45 patients with ages ranging from 31 to 88 years.	Prospective and observational. **Devices used:** Gas analyzer (ABL715 Series, Radiometer Medical ApS, Brønshøj, Denmark), Precision PCx glucose meter (Abbott Diabetes Care, Amersfoort, The Netherlands) and subcutaneous continuous glycemia monitoring system (CGMS System Gold; Medtronic MiniMed, Inc., Northridge, CA, USA). **Reference method:** Lab test. **Blood sample type:** Arterial.	**Accuracy and reliability:** The gas analyzer revealed satisfactory accuracy and precision in comparison with the reference method. The results of the continuous device had a significant correlation with the lab test. **Equipment handling-related factors:** The Precision PCx glucose meter showed a limited reliability with blood samples and test strips. The continuous system needs to be calibrated four times a day and its outputs are not immediate – they may take up to 24 hours to be available –, a characteristic that precludes its use in ICUs.

Author, year, country of origin, evidence level	Sample, age	Study design, glycemia measurement methods	Main results
Karon et al., 2014[46], United States, IV.	2,695 measurements, age not informed.	Two phases, retrospective and prospective. **Devices used:** ACCU Check Inform (Roche Diagnostics, Indianapolis, IN) and Nova StatStrip (Nova Biomedical Waltham, MA). **Reference method:** Lab test. **Blood sample type:** 95% from arterial catheter and 5% from venous catheter.	**Accuracy and reliability:** The AccuChek Inform glucose meter did not meet ISO precision guidelines. Its precision was lower than that of the reference method. The Nova StatStrip device showed a higher precision according to ISO 15197:2013 standards.
Shearer et al., 2009[47], United States, IV.	63 patients with an average age of 63.8 years.	Prospective. **Devices used:** Glucose meter (Sure Step Flexx, Johnson & Johnson, Lifescan Inc, Milpitas, California). **Reference method:** Lab test. **Blood sample type:** Capillary and from central venous catheter.	**Accuracy and reliability:** The glucose meter presented results that differed from the reference method in 20% of the measurements. Lab results differed significantly among the capillary and catheter blood samples. **Patient-related factors:** There was no association between the results from the glucose meter and hematocrit levels or average blood pressure.
Cook et al., 2009[48], United States, IV.	67 patients with an average age of 58.4 years.	Prospective. **Devices used:** Sure Step Flexx glucose meter (LifeScan Inc., Johnson & Johnson, Milpitas, California). **Reference method:** Lab test. **Blood sample type:** Capillary and from central venous catheter.	**Accuracy and reliability:** The glucose meter showed imprecision in comparison with the reference method. There was a difference of up to 20 mg/dL in the concentrations obtained for the two types of blood. **Patient-related factors:** The hematocrit level decreased the precision of the device.
Mann et al., 2008[49], United States, IV.	195 patients, age not informed.	Cohort. **Devices used:** Accu-Check Inform (Roche Diagnostics, Indianapolis, IN), Accu Check Advantage (Roche Diagnostics, Indianapolis, IN) and Medisense Precision PCx (Abbot Diagnostics, Aboot Park, IL). **Reference method:** Lab test and SureStep Flexx glucose meter (LifeScan, Milpitas, CA) to estimate error rates. **Blood sample type:** Arterial and venous blood.	**Accuracy and reliability:** The glucose meter outputs were higher than those obtained in the lab test. **Patient-related factors:** The hematocrit level contributed to errors in the glucose meter. Mathematical formulas can be used to calculate the correct values.

Author, year, country of origin, evidence level	Sample, age	Study design, glycemia measurement methods	Main results
Gijzen et al., 2012[50], United States, IV.	80 patients with an average age of 68.3 years, 390 measurements.	Prospective and observational. **Devices used:** Accu Check Inform II System, HemoCue Glu201DM, Nova StatStrip, Aboot Precision Pro and Menarini GlucoCard Memory PC. **Reference method:** Lab test. **Blood sample type:** Arterial.	**Accuracy and reliability:** The devices Accu Check Inform, HemoCue and Precision showed satisfactory precision and met ISO 15197 criteria. The opposite was observed for Nova StatStrip and Menarini GlucoCard. **Patient-related factors:** Hematocrit, sodium, potassium, nitrogen, bilirubin, total protein and albumin levels did not influence glycemia results.
Watkinson et al., 2012[51], United Kingdom, III.	206 patients with an average age of 56 years.	Clinical trial and prospective. **Devices used:** Precision PCχ, (Medisense glucose dehydrogenase, Maidenhead, United Kingdom) and HemoCue 201DM (glucose dehydrogenase, Angelholm, Sweden) glucose meters and Radiometer 700 (glucose electrode) hemogasometer. **Reference method:** Lab test. **Blood sample type:** Arterial.	**Accuracy and reliability:** HemoCue presented results similar to those obtained with lab tests. Both glucose meters were imprecise in comparison with the reference method. The outputs of the Radiometer device did not show a significant difference from lab test results. **Patient-related factors:** Whole blood glucose concentration, hematocrit, pH and oxygen levels can reduce the measurement precision.

Legend: ICU: intensive care unit; ISO: International Organization for Standardization; pH: potential of hydrogen.

DISCUSSION

The scientific production found on accuracy and reliability of glycemia monitoring methods evinced the following aspects: measurement method and sample type, characteristics of critically ill patients and equipment handling.

Measurement method and sample type

The analysis of the papers revealed 14 (77.7%) studies that reported comparisons between results of glycemia measurements obtained with glucose meters and lab tests, adopted as the reference method by the authors of the mentioned investigations[34,36-37,39-41,43-50]. Four (22.2%) studies, whose comparison methods were glucose meters and lab tests, claimed that the mobile device showed overestimated outputs which disagreed with the other procedure[41,44,46,49].

In addition, two (11.1%) publications considered the gas analyzer as the reference method[28,44] and two used the mobile glucose meter as the gold standard[38,42].

As for the blood sample type, the results showed that six (33.3%) studies focused on venous and capillary[36,39,43-44,47-48], four (22.2%) used arterial and capillary[35,37-38], two (11.1%) analyzed arterial and venous[46,49], four (22.2%) used arterial only[34,38,43-44], one (5.5%) explored arterial, venous and capillary[34] and one (5.5%) explored venous blood only, originated from central venous catheter and venous puncture[40].

It is important to emphasize that ISO 15197 criteria establish guidelines for the accuracy of glucose meters when their outputs are compared with lab test results. The criteria, published in 2003, indicate that at least 95% of the measurements must meet a maximum range of ± 15 mg/dL when glucose concentration is lower than 75 mg/dL; if the concentration is higher, the acceptable margin of error is turned into a percentage and adjusted to 15%. More recent guidelines[53] suggest intervals of ± 15 mg/dL for glucose concentrations lower than 100 mg/dL, and for higher levels the acceptable margin of error is converted into a percentage and adjusted to 20%. These criteria guided seven (38.8%) studies[35-38,41,46,50] in the sample, among which six exposed a disagreement with the norm.

These findings suggest that, despite the advantages of glucose meters, such as rapid response, easy handling, need for a low sample volume and low cost, the benefit from monitoring glycemia levels with these devices can be inferior to those obtained when lab tests are performed. Hence, taking into account the wide use of glucose meters in several health services, the authors suggest that healthcare professionals are careful when considering measurements with this type of apparatus if they are faced with low or high glucose concentration outputs. In these cases, it is important to discuss the possibility to check the results using other methods, such as lab tests, with the team. It is also necessary to contemplate patients' clinical conditions, which will support safe interventions oriented to glycemic control.

Regarding the blood sampling site, one (5.5%) study[39] used the ear as an alternative region to obtain capillary blood, in addition to the digital pulp, to evaluate if this change would lead to more reliable results. However, this alteration did not impact the precision of the device. Other seven (38.8%) investigations that resorted to capillary blood samples described collection through digital pulp puncture[34,36,37,43,43,47,48].

The presence of edema in critically ill patients can impair the assessment of blood absolute glucose concentration, because in patients in hypercatabolic state the proportion of glucose that reaches the body periphery is low, which makes capillary blood glycemia less representative of the processes in arterial compartments[54].

From another perspective, studies advise against the use of blood samples originated in central venous catheters given that there may exist a variation of up to 20 mg/dL in the glucose concentration in comparison with that found in samples obtained through venous puncture or from arterial blood[34,40,47].

Additionally, one (5.5%) study verified if there could be contamination by exogenous glucose in samples obtained from different sites and if it could influence the results. Although the findings did not point to contamination, they revealed differences between outputs whose samples originated from different vias (central venous catheter, peripherally inserted central catheter or venous puncture)[40]. Researchers claim that the most appropriate via to collect blood samples in critically ill patients is the arterial[20], followed by central venous catheter[55].

Subcutaneous continuous glycemia monitoring systems are considered effective because of their capacity to provide information about the trend, magnitude, duration and fluctuation frequency of blood glucose concentrations[56].

These devices were analyzed in three (16.6%) studies[35,42,45], which pointed to divergent results. The investigation carried out in Amsterdam in 2012[28] revealed that there may be technical problems, such as extra calibration requirements by the device, glycemia reading errors when measurements are performed before calibration and early withdrawal of the sensors because of alarms or noises that decrease the accuracy and reliability of these devices. The same study considered the apparatus more reliable when used with diabetic patients, given that their results were closer to those provided by the hemogasometer.

Price et al. (2008) reported that the continuous monitoring system is imprecise in comparison with glucose meters[42]. In the study by Corstjens et al. (2006) the outputs of the continuous device were not as accurate and reliable as those provided by glucose meters, but were similar to the outputs obtained in lab tests[42,45].

Recently, a clinical trial assessed the precision, feasibility and acceptance by the nursing team of a subcutaneous continuous glycemia monitoring device in 20 ICUs. The results showed that the accuracy of this system was lower when the amplitude of the glucose concentration was higher, that is, it did not work appropriately in cases in which the levels were relatively low or high[18].

Literature brings studies which evince that some drugs, such as acetaminophen and ascorbic acid, can influence glycemia results provided by continuous monitoring systems[57-58]. Some substances, among which maltose, xylose and icodextrin, also change the outputs of this apparatus. The latter caused an increase of more than 100 mg/dL in glucose concentration[59]. Another limitation for the use of continuous monitoring equipment is the imprecision in the measurements in the first 24 hours after the insertion of the subcutaneous sensor that results from local tissue inflammation[60]. These findings show that continuous monitoring systems require more tests so their feasibility can be evaluated better.

The Food and Drug Administration (FDA) advocates that insulin doses are determined according to blood glucose values instead of continuous monitoring systems, given that these use interstitial samples. The results of

the present review indicate that although continuous monitoring devices are an advanced and promising innovation in the field of glycemic control, there are not enough investigations on their accuracy and reliability to support their application in critically ill patients. In addition, it is estimated that their cost is higher, which will make it inaccessible to most ICUs in Brazil.

It is worth stressing that new continuous glycemia monitoring technologies are being introduced in ICUs services, such as continuous glycemia intravenous monitoring devices or spectroscopy-based equipment, in which the point-of-care apparatus is linked to a line proximal to the central venous catheter with a venous feedback; after collection and centrifugation of blood, the measurement is carried out through the interaction of the sample with infrared light and the output is displayed. This system was considered safe and precise for use in critically ill patients[61-63].

The present review also included two (11.1%) papers that described tests with hemogasometers, or blood gas analyzers, and compared their performance with other methods', such as subcutaneous continuous monitoring or glucose meters[46,60]. In these cases, the results were reliable. This finding is corroborated by a review study published in 2013[20].

Another study exhibited comparisons between lab tests and blood gas analyzers and emphasizes that their precision was similar, but taking into account the response time, sample volume and cost, hemogasometers seem to be a better alternative. The same investigation also demonstrated that there is no difference in the cost of the analysis of individual samples between this method and mobile devices[16].

It is noteworthy that gasometers demand as many maintenance procedures as other techniques and can be implemented only after the training of the ICU team, which can delay the sampling and input into the equipment. This last characteristic would probably lead to work overload and consequently more costs.

Nevertheless, blood gas analyzers can be considered a reliable and safe method in the care of critically ill patients, because they can be put inside or near ICUs, in addition to supporting other conducts by providing more parameters (pH value, partial pressure of carbon dioxide, potassium and sodium concentrations) which have to be monitored in this care setting.

Factors related to the characteristics of critically ill patients

Four (22.2%) studies[43-44,48-49] showed that altered hematocrit levels may affect the precision of glycemia measurements if lab tests are taken as the reference method. Three (16.6%) investigations[47,50-51] reported the opposite regarding the glucose meter performance.

The normal hematocrit levels ranged from 37% to 47% for women and 42% to 52% in men. Higher contents result in overestimated glucose concentrations, because the reduced level of red blood cells leads to a decrease in plasma displacement and consequently more available glucose for the chemical reaction with the enzyme immobilized in the measurement strip[57].

Still on the influence of hematocrit levels on glycemia analysis, one (5.5%) paper[49] proposed mathematical formulas for each equipment to decrease error rates resulting from this specific cause.

One (5.5%) study[43] mentioned edema as a condition associated with imprecision in glucose concentration outputs. Two (11.1%) evaluated if blood gases (pO^2) and pH could affect the results and found no evidence of

it[41,50]. Ginsberg (2009) conducted an investigation in that sense, based on the fact that glucose meter test strips are usually calibrated for capillary oxygen concentrations, and high oxygen contents, such as those found in arterial samples or patients who received oxygen, may result in lower glycemic values. A similar situation happens when low oxygen levels, such as those observed in venous samples or in patients with severe chronic obstructive pulmonary disease, may lead to inaccurately high outputs[64]. The study by Eastham et al. (2009) demonstrated that bilirubin, galactose, hematocrit, triglyceride and uric acid levels also interfered with the precision in glycemia measurements[65].

Administration of vasopressors (catecholamines) to hemodynamically unstable critically ill patients is common, and the use of this type of drug was associated with higher chances of measurement error in capillary samples in three (16.6%) studies[34,36,38]. According to literature, other substances, such as sedatives which induce blockage of beta-adrenoreceptors[66] and ascorbic acid (vitamin C)[67] can also conceal real glucose concentrations.

Although the mentioned factors may vary from patient to patient, healthcare teams must be cautious when faced with extreme glycemia levels. Before defining interventions, professionals have to know and evaluate patients' clinical conditions such as hematocrit level, respiratory parameters (pH, pCO^2), hemodynamic (blood pressure) and neurological stability, and ponder the use of other methods, for instance, lab tests and hemogasometer, to confirm the result.

Factors related to equipment handling

Two (11.1%) studies that addressed factors related to equipment handling focused on glucose meters and mentioned that the number of calibrations, the use of several batches of strips and lancets and the types of equipment used in the same unit[45,50] may interfere with the accuracy of glycemia results. These findings are similar to those reported in an investigation carried out in an emergency unit in which the "retest" was advocated; it has to be executed ideally ten minutes after the first measurement by the same professional and with the same equipment in case of critical glycemia levels to increase precision[68].

Other publications corroborate these statements and sustain that storage conditions of the test strips, including room humidity and temperature, sterilization of glucose meters after use when they have to be used with multiple patients[70-72] and equipment (glucose meters, blood gas analyzer, lab apparatus) calibration may influence the quality of measurements.

It is assumed that the contact of mobile devices with contaminated surfaces or excessive exposure of strips whose functioning is based on enzyme-catalyzed chemical reactions (glucose oxidase, peroxidase, hexokinase) may cause these enzymes to interact with confounding factors[42], which influences glycemia results that depend on photometric or amperometric devices.

It is noteworthy that usually clinical practice is not guided by standardization norms when it comes to collection vias, which causes nursing teams to choose puncture sites according to their preferences. Consequently, a single patient can present several collection sites, which may be a source of interpretation errors per se. The quality of the lancets used in the exams can also be crucial. In some institutions, the brand choice is based on cost issues, which does not always benefits patients.

In addition, some services cannot afford lancets and use smaller caliber needles to perform capillary punctures. There is no specific legislation addressing ideal materials for capillary blood punctures in ICUs; however, the Brazilian regulatory norm number 32 for health services advocates the systematic use of safety devices and materials appropriate to the practice to be carried out[72].

A researcher accidentally found out that collecting capillary blood after the hands of the person contacted sweets, cookies or fruits may cause glycemia levels to be erroneously high and be an important source of imprecision. Use of lotions and soap was tested but did not change the precision of the device[64].

It is considered that hand hygiene by healthcare professionals is essential and widely disseminated in infection prevention, but the paper by Ginsberg (2009) stresses the importance of this procedure also during glycemia checking, because improper hand washing or omission of it could interfere with the accuracy and reliability of glycemia results[64].

Some studies report that work overload in nursing teams may favor an unsafe care regarding the occurrence of infections, falls and administration of medication[73]; nevertheless, it is necessary to perform new investigations that show an association between work overload in nursing teams and accuracy and reliability in glycemia measurements.

It is estimated that, in clinical practice, aspects such as different sampling sites and measurement methods can be mixed in the same work shift and with a single patient. Additionally, these factors are affected by the clinical conduct of each professional, the lack of knowledge of the team of aspects which favor imprecision and unsafety, critical judgment, clinical reasoning, patients' clinical evolution and prognosis, use of glucose meters from different brands in the same unit and the absence of norms for procedures that support professionals' choices. This lack of consensus in clinical practice may provoke disorientation in the interpretation of how the glycemia condition is evolving.

The main contribution of the present study was to disclose the factors which influence the measurement of glucose concentrations in critically ill patients to guarantee accuracy and reliability in the results and patient safety. The review also spotted the lack of consensus on the recommendation of some measurement methods, a fact that can confuse healthcare teams. Future studies should be designed to assess the knowledge of ICU teams that provide care for critically ill patients and examine how the handling of interfering factors occur in different care settings.

FINAL CONSIDERATIONS

The accuracy and reliability of glycemia monitoring in critically ill patients is related to the devices used in the process, the clinical characteristics of patients (hematocrit and arterial gas levels, which provide information about the metabolic and respiratory situation of patients, and hemodynamic stability) and equipment handling, which can affect the outputs of the devices. The present review recommends that healthcare teams which work in ICUs are trained about the needs and clinical characteristics of their patients, the methods available in health services, including their advantages and limitations, and ponder their choices, taking into account their care reality and patient safety.

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