Reliability of continuous glucose monitoring system in the inpatient setting

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ABSTRACT

Aims/Hypothesis: Hyperglycemia and hypoglycemia are associated with increased morbidity and mortality in the inpatient setting. Standard point of care capillary glucose testing (POCT) is commonly used in hospitalized patients to monitor their glucose levels. The goal of this study was to examine the relationships between the glucose readings obtained by a continuous glucose monitoring system (CGMS) (Freestyle Libre) and the capillary blood glucose results obtained by the inpatient glucose POCT meter (Accuchek Inform II) as well as between CGMS readings and the serum glucose values obtained by the hospital laboratory. Study participants had either primary or secondary diagnosis of diabetes mellitus and were admitted to non-critical units. We hypothesized that there exists an acceptable agreement between the capillary blood glucose results obtained by the inpatient glucose POCT meter (Accuchek Inform II) and the readings obtained by the CGMS (Freestyle Libre); and that there exists an acceptable agreement between the serum glucose levels and the glucose values obtained by the CGMS.

Methods: This was an Institutional Review Board approved prospective cohort study for the non–critical inpatient setting. Fifty-two hospitalized patients with diabetes were recruited. After informed consent was obtained, patients were instructed on the application and use of the CGMS. The data were assessed using a standard regression analysis and modified Bland Altman analysis. All analyses were conducted using SAS, release 3.8 Enterprise Edition (SAS Institute Inc., Cary, NC).

Results: Fifty-two subjects recruited into the study represented a sample of convenience. There were a total of 467 AccuChek-Libre pairs, The regression analysis showed a negative bias between.

Libre and AccuChek, $R^2 = 0.83$, with Libre glucose readings on average being lower than those of AccuChek. Using Bland-Altman analysis, 42% of the 467 Libre-AccuChek pairs had a difference in glucose reading more than 15%. Mean absolute relative difference (MARD) between Libre and AccuChek was 15.6%; mean relative difference (MRD) between Libre and AccuChek was −11.4%.

The regression analysis showed a negative bias between Libre and serum glucose, $R^2 = 0.89$. Using Bland Altman analysis, 36% of the 44 Libre-serum pairs had a difference in glucose reading more than 15%. Mean absolute relative difference (MARD) between Libre and serum glucose was 13.2%; mean relative difference (MRD) between Libre and serum glucose was −12.5%.

A review of the data pairs showed that 71/467 Accuchek-Libre pairs had one result that was either below 70 mg/dl or above 200 mg/dl (combined American Diabetes Association-ADA-, American College of Physicians-ACP- and American College of Endocrinology-AACE- goals). Thus 85%, of these pairs would have yielded results that engendered the same intervention (e.g. treatment for hypoglycemia or hyperglycemia). Likewise 5/45 Serum-Libre pairs had one result that was either below 70 mg/dl or above 200 mg/dl; thus 89% of these pairs would have yielded results requiring the same intervention.

Conclusion/Interpretation: These findings confirm the existent literature and indicate acceptable agreement between the standard POCT and the CGMS as well as between serum glucose and the CGMS values. Because of the

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advantages of the CGMS over capillary blood glucose testing (reduced patient discomfort and reduced staff exposure to patients in isolation) CGMS use may be preferable to the current bedside capillary blood glucose testing in hospitalized patients with diabetes mellitus. As with other laboratory measures, clinical judgement needs to be exercised when the laboratory values are used to guide patient care.

Introduction

Uncontrolled diabetes mellitus increases morbidity and mortality in hospitalized patients. Avoiding significant hyperglycemia and severe hypoglycemia often requires complex insulin regimens [1–2] and necessitates point of care glucose testing (POCT) [3].

POCT, depending upon the patient's status, may be carried out from 4 times daily to hourly. POCT (due to the need to lance the finger) causes discomfort for the patient each time a capillary blood sample is obtained [2,4] because fingers are densely innervated [2,5–6] Considering that the continuous glucose monitoring systems (CGMS) are inserted only once in 14 days (barring the need for radiological tests or dialysis) they are less invasive and more comfortable than the fingersticks [7–8].

POCT requires a health professional to enter the patient room each time a glucose value needs to be obtained while CGMS require a patient-staff contact only twice in up to 14 days (when the sensor is placed on the patient's arm and when it is removed). This reduction in patient/staff contact may be advantageous in cases where patients need to be isolated because of contagious infection (such as COVID 19) and, in addition, may produce staff time savings, potentially improving cost-effectiveness of bedside glucose monitoring.

Studies have shown that CGMS improve glycemic control in the outpatient setting and reduce patient discomfort [1–2]. Randomized clinical trials done by Holzinger et al. and Galindo et al. showed that the risk of hypoglycemia decreased in hospitalized patient using CGMS [9–11] because CGMS help to identify the trends of hypoglycemia. This CGMS feature enables earlier intervention than is possible with POCT. Survey conducted by Boston Biomedical Consultants among ICU managers and nurses in 2007 showed that hourly blood glucose testing and finger pricking was found to be a major drawback in 30% of patients [12]. 93% of respondents cited nurse labor savings, 24% noticed improved patient comfort and about 38% of respondents expressed an interest in a CGMS device [12]. With real time glucose monitoring having visual displays, CGMS provide an increased opportunity for patients to get involved in their diabetes management [13]. A randomized clinical trial conducted in 23 European diabetes centers [1] showed that total treatment satisfaction score was significantly improved for the group using glucose sensing technology acknowledging the benefits of ease of use, comfort and ready ability to apply sensor information.

Until the COVID-19 surge, CGMS were not approved by the United States Food and Drug Administration (FDA) for in-patient use. This lack of approval reflects lack of studies demonstrating reliability of CGMS in hospitalized patients. In March 2020, the FDA provided an emergency waiver allowing the use of non-invasive continuous glucose monitoring in hospitals during the COVID-19 surge for the purpose of reducing clinical staff/patient contact as well in order to decrease the use of personal protective equipment (PPE) [14]. After the FDA waiver, limited studies have been carried out to explore the use of CGMS in both critical and non-critical patients [1,2,5,7,15,16].

With the emergence of potential benefits of CGMS in hospitalized patients {reduced patient discomfort and reduced patient/staff in-person interactions) additional studies are required to assess the accuracy and feasibility of CGMS in inpatient setting. We designed a prospective cohort study to examine the relationships between glucose results obtained by Libre CGMS readings and the existing standard (AccuChek Inform II) as well as between Libre readings and serum glucose (measured in the hospital laboratory) in non-critical patients at two New York City hospitals.

Methods

The Institutional Review Board approved a prospective cohort study. The study population consisted of non-pregnant adults (greater than 18 years old) with either a primary or secondary diagnosis of diabetes mellitus, hospitalized on non-critical units and not requiring dialysis. The participants were followed during their in-patient stay (2-14 days).

Upon completion of informed consent, the investigators instructed the patient on using the Freestyle Libre CGMS and placed the sensor on the back of the patient's arm. Patients used either a smartphone or a reader to obtain glucose values. Investigators informed patients that all medical intervention decisions will be made using the standard of care AccuChek Inform II.

Results from the Freestyle Libre CGMS were downloaded via a Librelink from the sensor, and those from the AccuChek Inform II and serum glucose were retrieved from the electronic medical record. All data were stored in the Research Electronic Data Capture (RED Cap) system.

Statistical Methods

Descriptive statistics (frequency distribution for categorical variables and mean, SD, median, interquartile range, minimum, and maximum for continuous variables) were calculated. These statistics were calculated for the actual measurements from the devices and for their paired

differences. All analyses were conducted using SAS, release 3.8 Enterprise Edition (SAS Institute Inc., Cary, NC).

Linear regression analysis was performed to calculate the formula and R-square between AccuCheck and Libre glucose readings and between Libre and serum glucose readings. Regression plot was used to visualize the correlation between AccuChek and Libre glucose readings and between Libre and serum glucose readings using ISO 15197:2013 criteria for results within ± 15 mg/dL or ± 15% for samples with glucose concentrations less than 100 mg/dL and ≥100 mg/dL, respectively [17].

A modified Bland-Altman plot was used to visualize the agreement between AccuChek and Libre glucose readings and between Libre and serum glucose readings using ISO 15197:2013 criteria where the meter system results were within ± 15 mg/dL or ± 15% of the mean reference POCT result for samples with glucose concentrations less than 100 mg/dL and ≥ 100 mg/dL, respectively [17].

Mean absolute relative difference (MARD) and mean relative difference (MRD) were calculated.

The data were plotted in two ways: standard regression analysis and modified Bland Altman. For the regression analysis, the Libre measurement (vertical axis) was plotted against the AccuChek measurement (horizontal axis).

For the modified Bland Altman plot, the arithmetic difference between Libre and AccuChek (vertical axis) was plotted against the AccuChek measurement (horizontal axis). Negative values correspond to the Libre measurements being lower than the AccuChek.readings. All graphs were plotted in mg/dl units. In order to apply the ISO standard to the difference, two separate pairs of reference lines were drawn. The horizontal reference lines represent the ± 15 mg/dL limits when AccuChek reading was less 100 mg/dL. The sloping lines represent the ± 15% difference when AccuChek reading was 100 mg/dL or greater.

Because the numerical differences do not always translate into differences in clinical decision making, we reviewed American Diabetes Association (ADA), American Association of Clinical Endocrinology (AACE) and American College of Physicians (ACP) glucose goals for hospitalized patients [18–20]. All of these guidelines defy hypoglycemia

as glucose concentration below 70 mg/dL. The acceptable upper limit of glucose concentrations can be as high as 200 mg/dL (ACP guidelines). We therefore developed the following criteria to establish when numerical difference is glucose concentration requires a difference in clinical decision making. If one member of a given Libre/POCT or Libre/serum pair was between 70 and 200 mg/dL, but another was outside of this range; or if one member of the pair was less than 70 mg/dL while the other was more than 200 mg/dL, the discrepancy was considered significant enough to affect clinical decision making. Using these criteria, a percentage of Libre/POCT and Libre/serum pairs where numerical difference required a change in clinical intervention was calculated.

Results

The final sample of 52 subjects was a sample of convenience. The mean age was 60 ± 11.7 years. Forty-one (79%) subjects were male, 24 (46%) were Black, 50 (96%) had type 2 diabetes and 2 (4%) had type 1 diabetes. Ten (19%) had been diagnosed with diabetes for less than 1 year, 11 (21%) between 1 and 5 years, 9 (17%) between 5 and 10 years, and 22 (42%) had at least 10 years since their diagnosis of diabetes. Five subjects (10%) had a primary diagnosis of diabetes mellitus. Of those with a secondary diagnosis of diabetes mellitus the top primary diagnoses included foot ulcers/infections, congestive heart failure, coronary artery disease or abnormal EKG.

There were a total of 467 AccuChek-Libre pairs and 44 serum-Libre pairs.

The regression analysis (Fig. 1A) showed a negative bias between Libre and AccuChek ($R^2 = 0.83$, Fig. 1A). The modified Bland Altman plot also showed a negative bias between Libre and AccuChek (Fig. 1B). On average, Libre glucose readings were lower than those of AccuChek. Forty two percent of the 467 Libre-AccuChek pairs had a difference in glucose reading more than 15%. Among the pairs where AccuChek reading was less than 100 mg/dL, 51% differed by more than 15 mg/dL. Among the pairs where AccuChek reading was greater than or equal to 100 mg/dL, 39% differed by more than 15%. Mean absolute relative difference (MARD) between Libre and AccuChek readings was 15.6%; mean relative difference (MRD) between Libre and Accuchek readings was -11.4%.

The regression analysis showed a negative bias between Libre and serum glucose ($R^2 = 0.89$, Fig. 2A). Modified Bland Altman plot demonstrated that 36% of the 44 Libre-serum pairs had a difference in glucose readings more than 15%. Among the pairs where serum glucose was less than 100 mg/dL, 33% differed by more than 15 mg/dL. Among the pairs where serum glucose was greater than or equal to 100 mg/dL, 37% differed by more than 15%. Mean absolute relative difference (MARD) between Libre readings and serum glucose was 13.2%; mean relative difference (MRD) between Libre readings and serum glucose was -12.5%.

Seventy one out of 467 Accuchek-Libre pairs had one result that was either below 70 mg/dl or above 200 mg/dl. Thus 85%, of these pairs would have yielded results that engendered the same intervention (e.g. treatment for hypoglycemia or hyperglycemia). Likewise 5 out of 45 Serum-Libre pairs had one result that was either below 70 mg/dl or above 200 mg/dl. Thus 89% percent of these pairs would have yielded results requiring the same intervention.

Discussion

As discussed in the introduction, POCT creates patient discomfort and endangers frontline health care workers by increasing staff exposure to particularly contagious patients (such as, for example, those with COVID-19), the issues which can be alleviated by the use of CGMS. Because of these potential advantages of CGMS, after FDA waiver for the use of CGMS in hospitalized patients was issued for COVID-19, limited studies were carried out to examine the reliability of CGMS in the inpatient setting.

Reutrakul et.al., examined the feasibility of CGMS during COVID-19 pandemic in non-critically ill patients [8]. This study, included 9 patients and compared the POCT and sensor glucose values using Dexcom G6 sensor. The authors found that the correlation coefficient of glucose values was 0.927. The study had small sample size, but the results suggested the feasibility of CGMS in noncritically ill hospitalized COVID-19 patients. Larger randomized clinical trials, however, are required for confirmation.

Holzinger et al. conducted a randomized controlled clinical trial in 124 mechanically ventilated critically ill patients which demonstrated that the mean CGMS and capillary blood glucose levels were not different between the CGMS group and control group (105.8 ± 18.1 and 110.6 ± 10.4 mg/dl respectively) [9]. The rates of severe hypoglycemia in a real-time CGMS group were lower (1.6% in the CGMS group vs 11.5% in a control group, $\rho = 0.031$). This difference was attributed to the fact that CGMS are able to track trends via automatic measurement frequencies ($\sim$every 5 min) [1–2,21–22]. Such technological approach, coupled with expedited intervention, decreases the morbidity associated with hypoglycemia [23]. POCT devices, being episodic, do not have this ability.

A randomized clinical trial by Singh et al. in 72 hospitalized patients, found that there was no difference in nocturnal hypoglycemia, time in target range (70–180 mg/dl) and time above target range between the CGM group and the POCT group [11]. The study revealed that there was no *prolonged* hypoglycemia in patients using CGMS when compared to POCT (which was performed four times a day). The authors concluded that CGMS effectively identified the trends of hypoglycemia and hyperglycemia which enabled earlier intervention than would be possible with POCT [5].

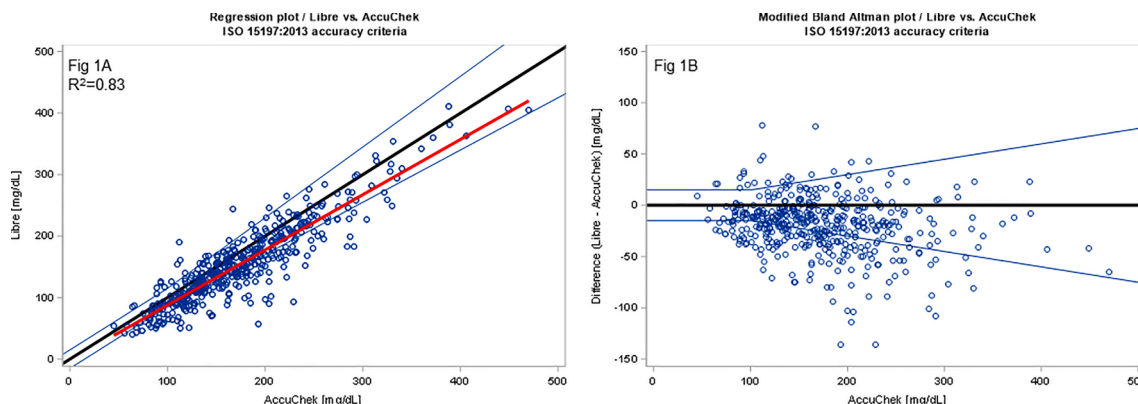In our study we have compared the interstitial fluid glucose result of

Fig. 1. A: Regression plots for AccuChek-Libre pairs; R2 = 0.83. Fig. 1B: Modified Bland Altman Plot for AccuChek-Libre pairs.
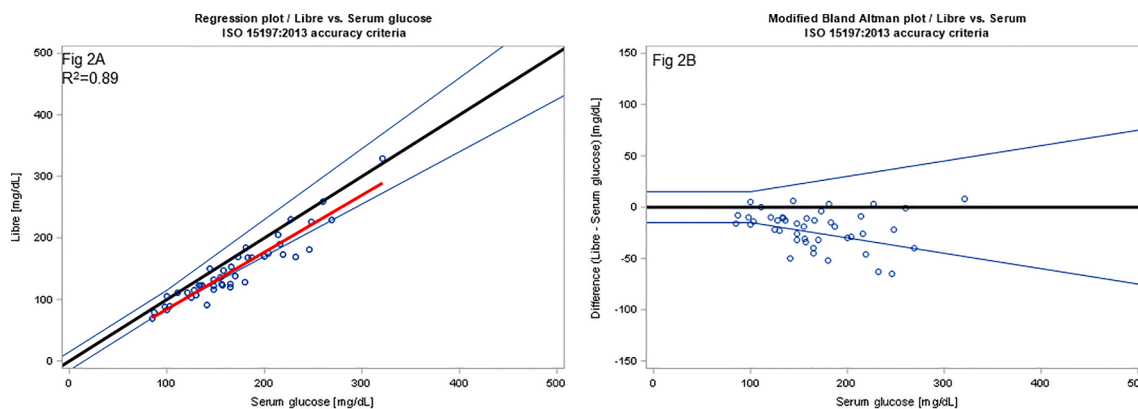
Fig. 2. A: Regression plots for Libre-Serum pairs; $R^2 = 0.89$. Fig. 2 B: Modified Bland Altman Plot of the Libre –Serum pairs.

the CGMS against that of the capillary blood glucose taken with the Accuchek Inform II and against that of the serum lab glucose result. We chose ± 15% difference between Libre and AccuChek or serum glucose because of the following considerations. Capillary blood (finger stick) and serum glucose may have a 10% to 12% difference in the fasting state, while in the fed state this difference can be as high as 10% to 25% [24–25]. The Food and Drug Administration (FDA) has allowed glucose meter values to be within 15% − 20% of laboratory measurements [26].

We found that ± 15% or 15 mg/dL agreement between Libre CMGS readings and either Accuchek or serum glucose was present about 60% of the time. In a similar study, Galindo et al found that overall 61.5% of their matched pairs were within 15% [7]. In two other studies 66% and 63% of pairs were within 15% difference [16,27]. Thus our results appear to be in agreement with those in the literature. Unlike our study, however, none of the previously published studies compared CGMS readings with serum glucose.

In the non-critical setting, the ADA, the AACE, the ACP recommend that the goal is to maintain the blood glucose between 70 and 200 mg/dl. Intervention is initiated for results below 70 mg/dl (hypoglycemia) or above 200 mg/dl. Using these criteria, we found that over 85% of the Accuchek–Libre pairs and Serum-Libre pairs would have engendered the same treatment even when numerical differences were present. According to the ADA 2021 Standards for Diabetes Care in the Hospital, clinical judgement with ongoing assessment of clinical status should be included into all patient decision making [18].

Cost effectiveness of any novel technology needs to be examined because, if the cost is prohibitive, the technology cannot be utilized even if it presents advantages over the existing approaches. To our knowledge, there are no studies addressing cost-effectiveness of CGMS in a hospital setting. Triki et al. published a cohort study involving type 1 diabetic ambulatory patients (N = 524) who were approved for CGMS. The authors found that there was no significant difference in outpatient medical services utilization. There was a decrease in emergency room visit rates from 30% to 19% and in the hospitalization rates from 22% to 12% during the study period from 2010 to 2016. The total cost incurred per patient, however, actually increased by about 25% among patients with high CGMS adherence. This increase was attributed to consumable equipment costs [28]. To our knowledge, at this time, there are no studies addressing cost-effectiveness of CGMS in a hospital setting.

Conclusion

We conclude that there appears to be an acceptable statistical agreement between CGMS readings and POCT AccuChek II readings and between Libre and serum glucose readings about 60% of the time. Over 85% percent of the time, even when a numerical difference between the glucose results obtained by different methods is present, clinical decision making is not affected. Given the potential advantages of CGMS

(reduced patient discomfort and reduced staff exposure to patients), CGMS may be preferable to POCT capillary blood glucose testing in hospitalized patients. Additional studies comparing both POCT glucose and CGMS readings to the "gold standard"-serum glucose concentration - are needed to further support a transition from POCT capillary blood glucose testing to CGMS. Cost effective studies should be included to assess financial feasibility. Like in cases of other laboratory measurements, clinical judgement must be exercised when glucose values obtained by any method are used to guide clinical decision making.

CRediT authorship contribution statement

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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