Response to Belalcazar and Swank

We read Belalcazar and Swank’s response (1) to our article with great interest. They have valid concerns regarding potentially biased estimates of treatment effects in small translational research studies where circumstances and environments are not as easily controlled as they are in efficacy-based research (2).

Our study (3) was a pilot, randomized, controlled trial of a multifaceted diabetes care intervention. Eleven primary care practices and their patients (n = 762), all from the same underserved community, were block randomized to one of three study groups before the start of the intervention. Practices were randomized instead of individual patients to ensure consistent delivery of the intervention for all patients and to eliminate contamination of the intervention between patients in the same practice (4).

Given the small number of practices randomized and the small sample of patients evaluated, the authors are correct that the study groups may be imbalanced with respect to several factors, even when the P values, which depend on sample size, are not statistically significant. To address this concern, we identified the most important and best “fitting” covariates (age, insulin, baseline metabolic value, study group, and the nesting of practices within study group) with a series of analytical techniques and a review of the literature and then adjusted for these variables when analyzing differences between study groups. We acknowledge the authors’ suggestion about adjusting for ethnicity; however, with 10 nonwhite subjects in the study, this was not feasible. Despite the small sample size, statistically significant differences between study groups were observed, lending further credence to our results.

The authors suggest using propensity scores to correct for differences in baseline characteristics among study groups (4). In observational studies, in which the selection of an intervention (e.g., insulin use) depends on various patient factors, using a propensity score, the estimated probability of receiving one of the interventions based on the patient-specific factors, can greatly reduce selection bias. As our study was a randomized controlled trial, we do not have variables that are truly related to the probability of receiving a particular intervention, since the interventions were randomly assigned a priori. Thus, a propensity score cannot be applied to this study. It may be possible to create an alternative composite score that would encompass several risk factors in future analyses of these types of interventions.

Variations on the multifaceted diabetes care intervention described in our article are currently being studied in a variety of settings, both locally and nationwide. Unfortunately, the majority of these efforts suffer from small sample size and a lack of randomization (5). In these studies, the use of propensity scores may enhance the validity of the results.

References


IGCs should be understood before considering continuous glucose monitoring (CGM) as a valuable and accurate alternative to track hyperglycemia and adapt insulin therapy. In addition, to use CGM in an optimal way, the device should provide real-time glucose concentrations in order to quickly adjust insulin infusion rates according to ambient glucose levels. This requires initial rather than post hoc calibration. These two key issues deserve further comment.

First, the <3-min lag time between subcutaneous and arterial blood glucose concentrations emphasized by the authors might be questionable in ICU patients. Indeed, such lag time depends on physiological parameters responsible for a different glucose kinetic between interstitial and plasma (2). Such kinetic difference has been shown to lead to spurious hypoglycemia in the general diabetic population (3). Most importantly, in critically ill patients, the kinetics of IGC may be affected by alterations in hydric/ionic balance, as revealed by the presence of a third compartment and subcutaneous edema and probably by many other factors that are still unknown.

Second, the good accuracy of CGM was not assessed when using the device GlucoDay in its most optimal manner. Indeed, real-time glucose levels ideally should be obtained to adjust insulin therapy as rapidly as possible. This objective could only be achieved if the GlucoDay is calibrated 2 h after insertion of the microfiber in the subcutaneous tissue, provided that glucose levels are stable enough. De Block et al. used post hoc calibrations with two or six points. Accuracy was considered as excellent and, as expected, better with the option of more frequent calibrations (4). However, as all calibrations were performed a posteriori taking into account all points together, results of accuracy might be overoptimistic. Whether the results would be as good when using CGM to obtain real-time glucose values, i.e., using a single calibration after 2 h (as recommended by the manufacturer) and adjusting progressively thereafter thanks to later calibrations, remains an open question.

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**References**


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**Intensive Insulin Therapy in the Intensive Care Unit: Assessment by Continuous Glucose Monitoring**

**Response to Radermecker**

We agree with Dr. Radermecker's (1) concerns regarding the applicability/accuracy of real-time continuous glucose monitoring (CGM) for adjusting insulin therapy in the intensive care unit (ICU). This was, however, not our aim, which was to document the duration/intensity of unacceptable glycemia in ICU patients (2). For this purpose, we used the best available method—a posteriori calibration. Since we observed that insulin therapy based on discontinuous glucose measurements failed to maintain normoglycemia, we suggested that it might be improved using online CGM.

Regarding the lag time between blood and interstitial fluid glucose, we acknowledge that both physiological parameters (equilibration of glucose across the capillary endothelial barrier) and device specifics (sampling frequency, microdialysis perfusion rate) should be considered (3). In a recent study, the delay between blood and glucose sensed by the GlucoDay was 7 min and mainly explained by instrument delay (6 min) (4). The lag time is consistent, irrespective of increments/decrements in glycemia and insulin levels (3). The hemodynamic alterations we encountered (hypotension, shock, vaso-pressor/inotropic need) did not worsen error grid analysis results (2). Such variables would rather affect subcutaneous glucose recovery/microdialysis, resulting in a calibration issue, rather than in a sensor performance issue. A lag time of <10 min is clinically acceptable, since online adjustment of insulin dose should be based on immediate detection by CGM of unacceptable rates of change (>25 mg·dl⁻¹·h⁻¹).

Criteria for evaluation of CGM performance and calibration are urgently needed. CGM accuracy improved after 6 instead of 2-point calibration (2). Calibration should be performed in times of glucose stability (<10% change over 9 min), a paradigm used in the GlucoDay. From our preliminary results, it seems that for real-time CGM, a single calibration after 2 h is not satisfactory and that verification using conventional glucose measurements is still mandatory. Whether progressive adjustment using later calibrations improves accuracy needs further investigation.

The use of continuous glucose–error grid analysis to evaluate clinical accuracy of CGM systems for ICU patients use is open for discussion (4) and might need adjustment. Insulin therapy in the ICU aims to titrate glycemia in a tight range (80–110 mg/dl), and changes of >25 mg·dl⁻¹·h⁻¹ (0.4 mg·dl⁻¹·min⁻¹) already require a change in insulin dose (5). The currently used boundaries of 1 mg·dl⁻¹·min⁻¹ are therefore not rigorous enough.

Hopefully these observations will stimulate a debate on current glycemic monitoring, the choice of dynamic boundaries for rate–error grid analysis, the need for standard methods to assess accuracy, and the definition of valid requirements for CGM systems in the ICU.

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