

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 interstitium 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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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, vasopressor/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 ($>25 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$).

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 $>25 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$ ($0.4 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$) already require a change in insulin dose (5). The currently used boundaries of $1 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{min}^{-1}$ 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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Chromium Picolinate Supplementation Attenuates Body Weight Gain and Increases Insulin Sensitivity in Subjects With Type 2 Diabetes

Response to Martin et al.

In a recent article of *Diabetes Care*, Martin et al. (1) reported their findings of attenuation of weight gain in subjects with diabetes who were given 1,000 µg chromium in the form of chromium picolinate (CrPic) in combination with 5 mg glipizide, a sulfonylurea drug. Over the 24 weeks of cotherapy, the weight gain values were 0.0 and 1.3 kg for glipizide plus CrPic versus glipizide plus placebo, respectively.

From Fig. 2 of the article, it is appar-

ent that all of the differences in body weight values at the end of the study were caused by an acute weight loss averaging 1.2 kg, which occurred within the 1st week after CrPic was started. Given that the SE was 0.5 kg, it is possible that some of the subjects lost as much as 3.0 kg in 1 week. Acute weight loss and a final weight difference between treatment and control subjects were not reported in other studies using 800–1,000 µg CrPic (2–5); thus, the results in the most recent study are evidence to suspect a drug-supplement interaction. As the article in question provides no discussion of the acute weight loss or any report of adverse events, it is not possible to know whether diarrhea, anorexia, or some other symptom was responsible for the weight loss. One of the other chromium studies (5) reported two subjects discontinuing the study because of gastrointestinal adverse effects, and glipizide adverse experiences are known to include diarrhea and other gastrointestinal symptoms.

In addition to not addressing the cause of the acute weight loss, Martin et al. presented but did not discuss a trend for an increase in triglycerides in the group receiving chromium. While the change of 30 mg/dl from baseline was not statistically significant, possibly because the treatment group was small, the increase from baseline in the placebo group was only 4 mg/dl. Earlier clinical trials of 800–1,000 µg chromium as CrPic, did not report an increase in triglycerides (2, 4, 5); therefore, again, a drug-supplement interaction is possible and needs be explored, even though the association of cardiovascular disease with sulfonylurea drugs has been discounted (6).

One possible explanation for the reason that the body weight loss effect reached a plateau after 1 week would be an adaptive lessening of chromium absorption. Timely measures of serum and urinary chromium would have helped understand whether a brief period of elevated serum chromium, in combination with glipizide, caused gastrointestinal adverse effects resulting in acute weight loss.

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D.A.M. holds stock in Pfizer. Pfizer is a manufacturer of the sulfonylurea drug used in the study D.A.M. is commenting on.

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Chromium Picolinate Supplementation Attenuates Body Weight Gain and Increases Insulin Sensitivity in Subjects With Type 2 Diabetes

Response to Mark

We thank David Mark for his comments (1) about our study (2) in which subjects with type 2 diabetes, who were given 1,000 µg chromium in the form of chromium picolinate (CrPic) in combination with 5 mg glipizide