Do Different Glucose Levels at Calibration Influence Accuracy of Continuous Glucose Monitoring Readings *in Vitro*?

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Two limitations shared by all continuous glucose monitors (CGMs) are poor accuracy in the hypoglycemic range[1] and poor accuracy when glycemia is changing rapidly.[2] This raises the issue of whether aspects of the calibration procedure could improve sensor accuracy in the hypoglycemic range. Retrospective analysis of CGM readings using *in silico* (i.e., computer-based) modeling suggest that the glucose levels at which calibrations are performed affect the performance of CGMs.[3–5] The purpose of this study was to determine whether the intrinsic accuracy *per se* of CGMs also improves in the low glucose range if multiple calibrations are performed at different and low glucose concentrations *in vitro*. Twelve sensors (Sof-sensor®; Medtronic, Northridge, CA) were exposed to three calibration conditions using Paradigm® 722 REAL-Time CGMs (Medtronic, Northridge, CA) following a randomized counterbalanced design. Each CGM was calibrated and tested in glucose solutions prepared in a Krebs physiological bicarbonate buffer at 37 °C and pH of 7.4. Since Paradigm 722 REAL-Time CGM units must be calibrated four times daily, with several calibration points rather than only the most recent calibration value being used for calibration, each unit was calibrated four times in a 144 mg/dl solution (144/144/144/144 mg/dl) or calibrated four times in 72, 144, or 216 mg/dl solutions following the sequence 144/72/216/144 mg/dl or 144/216/72/144 mg/dl, with a 40 min period between each calibration. Then, the units were tested by transferring the sensors to a 40-mg/dl solution and data compared when glucose readings reached stable levels. A one-way analysis of variance with repeated measures and Bonferroni *post-hoc* tests were adopted to compare calibration protocols (results expressed as mean ± standard error of the mean, $p < 0.05$). All sensors significantly overestimated the low glucose solution to a similar extent, irrespective of whether multiple calibrations were performed at the same or different glucose levels including one of the calibrations entered at a low glucose concentration (72 mg/dl; **Figure 1**; $p > 0.05$). There were also large mismatches between the CGM and reference glucose associated with the CGM's lag, most notably during the initial rapid fall in glucose levels (5–15 min; **Figure 1**) but no differences in the magnitude of these mismatches between calibration protocols at 5, 10, and 15 min as well as with the lag time defined as the time required for CGM glucose readings to decrease by half of the absolute change in reference glucose concentration (**Figure 1**; $p > 0.05$). However, since the glucose level of the last calibration solution was matched for all calibration protocols, we examined whether different glucose levels at the last calibration step affect accuracy and found that CGMs calibrated at 72 mg/dl misread the 40 mg/dl

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Abbreviations: (CGM) continuous glucose monitor

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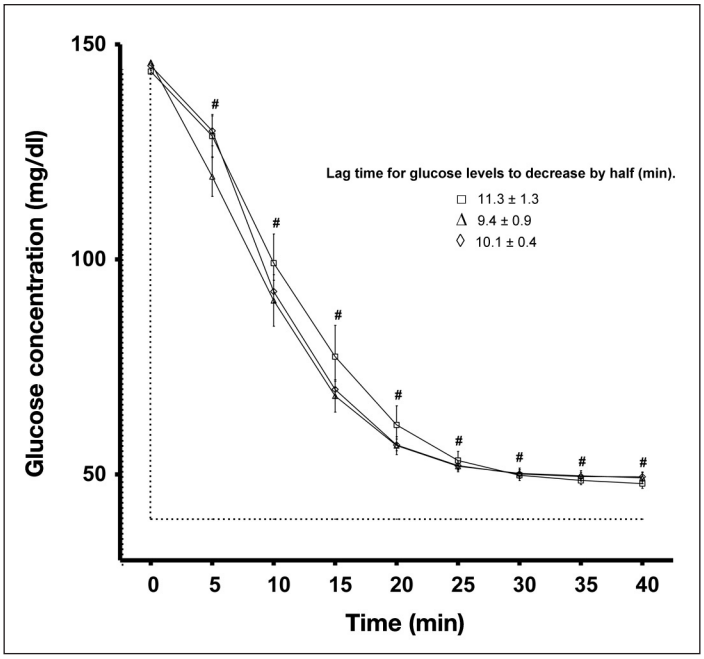

Figure 1. Effect of calibration protocol on CGM glucose measurements during an immediate fall in glucose concentration (from a 144 to 40 mg/dl solution). Repeated calibration at 144/144/144/144 mg/dl (□), 144/72/216/144 mg/dl (Δ), or 144/216/72/144 mg/dl (◊).

solution to a lesser extent (3.6 ± 1.8 mg/dl) compared to CGMs calibrated at 144 mg/dl (12.6 ± 1.8 mg/dl; $p < 0.05$) and 216 mg/dl (16.2 ± 1.8 mg/dl; $p < 0.05$). This indicates that the accuracy of the CGM tested here was influenced by the glucose level at which the last calibration was performed, thus corroborating, in part, the findings based on computer-based modeling.[3–5] However, given the evidence that CGM performance *in vivo* is poorer than *in vitro*,[6] it remains to be tested whether calibration at different glucose levels might be even more beneficial *in vivo* than reported here *in vitro*.

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