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Analysis: High-Tech Diabetes Technology and the Myth of Clinical "Plug and Play"

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Abstract

In this issue of *Journal of Diabetes Science and Technology*, Davey and coauthors present encouraging data that even short-term use of a real-time continuous glucose monitor can lead to marked reduction in hypoglycemia exposure. In this analysis, two particular issues will be discussed: the distinction between short- and long-term experiences with sensors and the use of standardized diabetes treatment algorithms for use with continuous glucose monitoring (CGM) devices. An understanding of both of these aspects of CGM devices is necessary for placing clinical diabetes technology products into the context of how they will be used in "real life."

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When the first generation of *blinded* retrospective continuous glucose monitoring (CGM) devices gave way to *real-time* CGM in the middle of the last decade, there was initial hope in the clinical diabetes community that we were witnessing the beginning of the end of hypoglycemia. Our initial (and admittedly naive) enthusiasm was somewhat tempered, however, as we became familiar with the sobering realities of sensor inaccuracy, sensor lag, and false alarms. While recent large-scale clinical trials[1–3] have demonstrated the efficacy of CGM to improve metabolic control in subjects with type 1 diabetes, we have also learned that the devices can be complicated, and their acceptance among patients is far from universal.

Into this current atmosphere comes the report by Davey and colleagues,[4] who considered that previous studies of CGM may have chosen alarm thresholds that were too low to account for sensor lag and inaccuracy, and that furthermore, subjects might require specific treatment instructions to prevent hypoglycemia following an alarm. They chose a slightly higher alarm threshold than other studies (80 mg/dl), which provided an additional "cushion" to prevent hypoglycemia in the face of an inaccurate sensor and/or rapidly falling glucose. Their treatment algorithm also accounted for the clinical context of the low alarm: 15 g for a standard alarm and 30 g for a low alarm following exercise or when "insulin was expected to be peaking." Compared to 3 days of blinded sensor wear, the subjects using unblinded sensors in real-time experienced a 64% reduction in CGM levels <65 mg/dl and a 44% decrease in CGM-defined episodes of hypoglycemia, without an accompanying increase in mean glucose. The marked decrease in time spent in hypoglycemia (307 vs 155 min) without an average increase in mean glucose suggests that the use of the high alarm in this study (200 mg/dl) also played a role in limiting hyperglycemia exposure.

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Abbreviations: (CGM) continuous glucose monitoring, (DATA) DirecNet Applied Treatment Algorithm, (DirecNet) Diabetes Research in Children Network, (MDI) multiple daily injection

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At first read, the generalizability of these findings seems limited. Despite the randomized controlled study design, the study highlights the *best* that available sensors can achieve, but without the practical obstacles that makes their continued use challenging. The short duration of the monitoring period does not take into account the sensor fatigue seen in the longer duration studies. In the Juvenile Diabetes Research Foundation study, for example, while average sensor wear remained about 120 h per week in the adult group, it fell in the childhood group to <100 h per week by 6 months and in the adolescent/young adult group to <80 h per week.[2] Furthermore, in the Davey study, setting the low glucose alarm to 80 mg/dl resulted in a false alarm rate of 62%. It is difficult to imagine continuing to use an alarm when 2 out of 3 alerts would result in a confirmatory blood glucose check in the normal range. The authors are careful to point out that this high rate of false alarms would be incompatible with routine home use, but suggest that limited use of this alarm threshold may be beneficial during periods of heightened hypoglycemia risk (exercise, hypoglycemia unawareness).

However, this study does raise the very practical and generalizable issue of patient education for diabetes technology devices and products. The use of formalized treatment algorithms for insulin dosing and/or hypoglycemia treatment/prevention in CGM trials has been uncommon. Given the demanding and intensive training required for even the basic *technical* aspects of sensor training, such as insertion, calibration, lag phenomenon, and downloading, more *clinical* areas of sensor use, such as insulin dosing adjustment and hypoglycemia treatment/prevention, for the most part have been handled individually and idiosyncratically, during the follow-up visits as the need arises. It is unclear, then, to what extent the demonstrated success or failure of CGM in the various trials has depended on the effectiveness of the algorithm itself or in its implementation and adoption by the subjects utilizing the technology; in other words, can we evaluate the true effectiveness of CGM without the ability to evaluate the effectiveness of our algorithms?

The Diabetes Research in Children Network (DirecNet) tried to examine this question in a pilot trial of the Abbott FreeStyle Navigator® (Abbott Diabetes Care, Inc., Alameda, CA) in two groups of children: a 30-subject cohort of pump users[5] and a 27-subject group on multiple daily injection (MDI) regimens.[6] These trials demonstrated some hemoglobin A1c–lowering effect of CGM in both the pump- and MDI–treated children but no significant impact on hypoglycemia, but were quite limited by the absence of a control group. What is particularly notable about these studies was the use of a protocol-specified approach to subject education, insulin dosage adjustment, and response to hyperglycemia and hypoglycemia: the DirecNet Applied Treatment Algorithm (DATA). The use of the DATA guaranteed at least some measure of standardization among study subjects in terms of education and response to common clinical scenarios. The absence of benefit of CGM with regard to hypoglycemia with this algorithm may have been related to the smaller carbohydrate doses for actual (15 g) or impending (10 g) hypoglycemia and the lack of accounting for exercise or timing of insulin action. An analysis of the use and acceptance of the DATA algorithm[7] showed that while subjects and parents relied at least initially on the DATA algorithm for dose adjustment and response to alarms, this reliance waned over time as they became more comfortable and confident, at which point they adapted the DATA algorithm for their own individual use. In effect, the standard algorithms were useful in the early phase of clinical use, when subjects were unfamiliar with CGM data. Later, with increasing familiarity, they substituted their own empirically derived solutions in the place of the standardized instructions. The diabetes educators charged with training subjects and families on the DATA algorithm found that insulin dosing and algorithm instruction were among the most time-intensive and difficult topics in the sensor training.[8]

Of course, the full potential of CGM to prevent or improve diabetes control and ameliorate or prevent hypoglycemia has only begun to be explored .[9] A commercial sensor-augmented insulin pump that suspends insulin delivery for sensor-determined hypoglycemia is now available, and introduction of hypoglycemia prediction software will allow for the next generation of sensor-augmented insulin pumps that will suspend insulin delivery for impending or predicted hypoglycemia with a minimum of false alarms. Initial studies of such systems have shown promise in both simulated[10] and actual clinical experiments.[11] However, until fully automated systems replace our current reliance on "clinical" algorithms to translate CGM data into meaningful insulin dosing instructions, they should undergo the same types of rigorous performance evaluation as their automated counterparts.

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