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# Combining Insulin Pumps and Continuous Glucose Monitors; Where Are We to Go from Here?

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## Abstract

Insulin pump development started in 1978, with the first commercially available glucose sensor marketed in 1999. Combining these two instruments is a logical step toward the closed loop. This article discusses three questions: Is pump development complete? How can a pump and a sensor be combined? Can the delay problem associated with the subcutaneous–subcutaneous approach for the closed loop be overcome?

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The widely cited meta-analysis on insulin pump therapy by its inventor, John Pickup, noted 0.51% lower hemoglobin A1c (HbA1c), 27% less fluctuation in blood glucose values, and 14% lower insulin doses associated with the use of insulin pump therapy.[1] However, trials analyzed in this article almost exclusively used regular human insulin and neutral protamine Hagedorn (NPH) combinations as the comparator injection regimens. When we meta-analyzed papers using rapid-acting insulin analogues as mealtime insulin and NPH as basal insulin, the advantage in terms of HbA1c was 0.35%,[2] and two recent trials using a rapid-acting insulin analogue as mealtime insulin and glargine as basal insulin could not establish a clear advantage for insulin pump therapy in adults.[3,4] Therefore, the insulin pump awaits further development to reestablish its advantage over injection regimens and its position as the gold standard for insulin delivery. One possible avenue is miniaturization. In the United States, the Omnipod® minipump is available (Insulet Corporation, Bedford, MA). This instrument is 44% smaller than currently available conventional insulin pumps and obviates the need for a catheter between the pump and the skin insertion site, while needle insertion is claimed to be less painful than with conventional insulin insertion sets. This claim and the impact on intermediate diabetes outcomes and quality of life need rigorous scientific investigation. To illustrate that every technical development needs stringent validation, one may look at the recently published evaluation of a mealtime bolus alarm added to an insulin pump. In a randomized clinical trial with 48 youth participating, the number of missed mealtime bolus administrations diminished from

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**Abbreviations:** (HbA1c) hemoglobin A1c, (NPH) neutral protamine Hagedorn

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baseline to 3 months, but this diminishment was not statistically significant anymore after 6 months, while HbA1c was not affected at any of the two time points.[5] Thus, not every technical development is an improvement and can turn out to be a gadget.

However, the first published results on the Guardian® REAL-Time system, a continuous glucose monitor (Medtronic, Sylmar, CA), are very promising. In a 162-patient, 3-month, three-arm randomized clinical trial, continuous use of the Guardian REAL-Time system lowered HbA1c by 0.6% more than in the control group, while the intermittent use group showed a lowered HbA1c in between—not significantly different from the control group. Hypoglycemia was also lowered, but not as impressively as one might have expected.[6]

The logical next step is combination of an insulin pump and a continuous glucose monitor in one instrument. Medtronic is the first company to market such an instrument, the Paradigm® REAL-Time system. This includes an insulin pump, a continuous glucose monitor, and a mealtime bolus wizard. Randomized clinical trials with the instrument include the recent STAR1 trial and the ongoing Eurythmics and STAR3 trials. STAR1 did not show an improvement in HbA1c or severe hypoglycemia, although time in hypoglycemia was diminished.[7]

With the combination of an insulin pump and a continuous glucose monitor, practical questions come up, such as what is the minimal distance from a continuous glucose monitor at which insulin can be infused? This is the subject of two investigations run by independent research groups.

A more fundamental question posed by Roman Hovorka is whether the subcutaneous–subcutaneous approach for the closed loop can ever be realized given its inherent delays.[8] The absorption of insulin injected subcutaneously takes 50 minutes, the physiological delay between receptor activation and insulin production is about 30 minutes, and the delay between plasma and interstitial glucose is estimated anywhere between 0 and 30 minutes, so if one takes this to be 10 minutes and adds a transport lag of 15 minutes for the typical continuous glucose monitor, this all adds up to 105 minutes. There are several ways to shorten this delay. Peak absorption of Technosphere® insulin (MannKind Corporation, Valencia, CA) takes 20 rather than 50 minutes.[9] Using curve fitting, we found no delay between interstitial and plasma glucose.[10] Many studies reporting longer delays applied an acute increase in glucose and used first-order kinetics modeling. Thus, they may not have been able to dissect distribution time from a possible delay between plasma and interstitium. Finally, the instrumental delay for some of the continuous glucose monitors is already close to 0 minutes. Taking all this together, the overall delay may be brought down from 105 to 50 minutes. Whether this will allow for a useful closed loop system still needs to be determined. For the moment, the most important decision making still is done by the patient.

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