Closed loop control for type 1 diabetes
Shows promise in a research setting, but needs further development in practice

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In the linked randomised crossover studies (doi:10.1136/bmj.d1855), Hovorka and colleagues compare the safety and efficacy of overnight closed loop insulin delivery with conventional insulin pumps in adults with type 1 diabetes. Automated closed loop control, known as an “artificial pancreas,” has the potential to greatly improve the health and lives of people with type 1 diabetes. The idea is not new—it can be traced back to developments that took place decades ago, when studies using intravenous glucose measurement and infusion of insulin and glucose showed that external blood glucose regulation was possible. Although these systems resulted in excellent glucose control, they were cumbersome and unsuitable for long term or outpatient use.

With the advent of minimally invasive subcutaneous continuous glucose monitoring, research and drug company efforts have been focused on the development of subcutaneous artificial pancreas systems. These systems link a continuous glucose monitor and a subcutaneous insulin infusion pump via a control algorithm, which retrieves continuous glucose monitoring data in real time (for example, every five minutes) and uses a mathematical formula to compute insulin delivery rates that are then transmitted to the insulin pump. So far, several studies have reported encouraging results. Almost all of the studies reported that closed loop control was better than standard insulin infusion pump treatment in terms of three outcomes: increased time within a target range, reduced incidence of hypoglycaemia, and better overnight control.

Hovorka and colleagues report two randomised crossover clinical trials that looked at 24 adults with type 1 diabetes to compare the safety and efficacy of overnight closed loop insulin delivery with that of conventional insulin pump therapy. The two protocols used a medium sized meal (60 g carbohydrate) or a large size meal (100 g carbohydrate plus alcohol). As in previous studies, closed loop insulin delivery significantly increased the time that plasma glucose was in the target range (3.9-8.0 mmol/L). In the context of ongoing research these trials have several new features:

Firstly, the randomised crossover trial design is virtually unique in the field of closed loop control. Because this design is the gold standard for clinical research, the results set a benchmark for future studies. The only other randomised controlled trial of closed loop control was recently presented at the 4th International Conference on Advanced Technologies and Treatments for Diabetes. This study recruited 24 adults and adolescents with type 1 diabetes in the United States and in France and achieved results similar to those reported by Hovorka and colleagues—more time within the target range of 3.9-10 mmol/L and a threefold reduction in hypoglycaemia.

Secondly, the control algorithm used by Hovorka and colleagues belongs to an advanced class of closed loop control technologies known as model predictive control. Algorithm designs for closed loop control have generally used either proportional-integral-derivative control or model predictive control. Proportional-integral-derivative control algorithms are reactive, responding to changes in glucose levels with adjustment in insulin delivery. Model predictive control algorithms are built over a model of the human metabolic system. Such algorithms are therefore proactive and insulin can be delivered in anticipation of changes in glucose concentrations. This compensates partially for the time delays inherent in subcutaneous glucose control (the time delay in insulin action, which can amount to 60 minutes or more). For this reason, model predictive control has become the approach of choice more recently. The algorithm developed by Hovorka and colleagues has certain distinct features, such as real time adaptation of the underlying model to changing patient parameters implemented as a selection from several predefined models. However, because details have not been given in this or previous publications, this potential advantage remains to be evaluated.

Thirdly, this is one of the first studies to test realistic meal scenarios and challenge the participants with a large dinner that included alcohol. As such, the study is a clear advance in the quest for an ambulatory artificial pancreas.

However, as the authors admit, one limitation is the exclusively manual control of the closed loop control system. The closed loop control system relied on study personnel to transmit data manually from the continuous glucose monitor to the computer running the closed loop control, and to transmit insulin injection recommendations from the computer to the insulin pump. In fully automated systems these processes are handled by data transmission and pump control devices, respectively. The
authors used manual control in their previous trials for well known reasons, including technological and regulatory barriers. However, manual transfer of continuous glucose monitoring data and manual control of the insulin pump place human factors into the closed loop control system and limit the investigation to testing only the control algorithm, not the closed loop control system as a whole. The testing of other key components, such as sensor-pump communication and error mitigation, would require much more effort and thorough system validation. Studies using fully automated systems have already been reported and offer hope for the future of ambulatory systems.

Finally, despite the sophistication of the control algorithm and the significant reduction in nocturnal hypoglycaemia, four episodes of severe hypoglycaemia (<3mmol/L) occurred, three of which the authors thought were attributable to the preceding prandial insulin dose and could not be prevented by the closed loop suspending insulin delivery. This finding reinforces the recently proposed idea that a dedicated hypoglycaemia safety system—a separate algorithm responsible solely for the assessment and mitigation of the risk of hypoglycaemia—may need to accompany closed loop control. Such safety systems already exist, and have proved useful.

In conclusion, closed loop control is in its infancy, with the first in-clinic studies now being reported. Preliminary results have been promising—the most notable improvement is in overnight control of type 1 diabetes, with improvements in safety and a reduction in nocturnal hypoglycaemia being reported. These improvements result from the fine adjustment of insulin delivery provided by closed loop control overnight being superior to a generally fixed basal rate and less likely to cause hypoglycaemia. The first application of closed loop control is therefore likely to be in glucose regulation overnight, a step that has the potential to improve dramatically the safety of insulin delivery during crucial, generally unsupervised, periods.

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