Enlarging the loop: closed-loop insulin delivery for type 1 diabetes

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A growing number of clinical trials have shown that home use of hybrid closed-loop insulin delivery systems reduces time spent in hypoglycaemia and improves time in target ranges for those with type 1 diabetes.[1–6] In September, 2016, the first commercially available hybrid closed-loop insulin delivery system for management of type 1 diabetes was approved by the US Food and Drug Administration for patients aged 15 years and older. Approval of this system was supported by a non-randomised trial in which the primary outcome was safety.[5,6] Yet, evidence on use of these systems in preadolescents falls short,[7,8] as does the inclusion of patients with suboptimal glycaemic control. Previous clinical trials have often poorly represented the real-world population of those living with type 1 diabetes. Data from the Type 1 Diabetes Exchange indicate that fewer than 30% of patients achieve glycaemic targets, with even lower frequency in youth and emerging adults.[9] Therefore, it is inherently difficult to generalise the results from many hybrid closed-loop trials to the more heterogeneous population living with type 1 diabetes. Furthermore, insurance coverage of these devices might be impeded if patients requesting such systems do not mimic the characteristics of the participants in a trial.

In *The Lancet*, Martin Tauschmann and colleagues[10] report the findings of a 12-week free-living, randomised controlled trial comparing hybrid closed-loop with sensor-augmented pump therapy in patients aged 6 years and older with suboptimal control, defined as screening glycated haemoglobin (HbA_{1c}) of 7·5–10·0%, of type 1 diabetes. After a 4-week run-in phase to assess device compliance, 46 participants were randomly assigned to hybrid closed-loop therapy and 40 patients to sensor-augmented pump therapy. In both groups, participants' ages ranged across the entire lifespan.

The primary endpoint, the proportion of time within target range (defined as 3·9–10·0 mmol/L), was approximately 11% higher with hybrid closed-loop use than sensor-augmented pump therapy (95% CI 8·2–13·5; p<0·0001). These findings held true across all age groups (<13 years, 13–21 years, and ≥22 years). Importantly, in subgroup analysis of those with HbA_{1c} of more than 8·5% at baseline, time in range increased by nearly 20% in the hybrid closed-loop group, which was more than six times higher than what was achieved in the control group. Although the increase in time in target range was greater with hybrid closed-loop therapy, the difference in HbA_{1c} between the two groups was modest, at 0·36% (95% CI 0·19–0·53; p<0·0001): a change that is similar to that shown in other smaller trials.[4,11] The fact that time within range provides a wealth of data that cannot be gleaned from single or multiple HbA_{1c} measurements highlights the meaningfulness of this metric both in clinical practice and as a research outcome.

Unsurprisingly, participants in the hybrid closed-loop group had more frequent, unscheduled contacts with study staff, probably related to technical issues, as the authors highlight in their discussion of the study limitations. Although a commercial product would probably overcome many of these difficulties, patients will still be responsible for filling the pump's insulin reservoir and changing the insulin infusion sets. Infusion set failure was responsible for the single episode of diabetic ketoacidosis in the hybrid closed-loop group. Current methods for detection of infusion set failures, namely patient education, will need to be replaced, or at least supplemented, by algorithms to help to alert patients to such an event promptly, to avoid serious outcomes.[12,13] The development of adjunctive components that would enable the prompt detection of an infusion set failure, which is a common event even for those using conventional pump therapy, remains a crucial problem to be addressed in future trials.

In the current study, the total daily dose and bodyweight were not significantly different from the screening value between groups. However, it is possible that both the sample size studied and the duration of follow-up might have hampered the ability to detect whether long-term use of these systems would have resulted in a difference between groups. Recognising that the obesity epidemic has not spared those with type 1 diabetes, it will be crucial to follow weight changes as these devices become more commonplace in clinical practice.

Amelie Benoist/BSIP/Science Photo Library

Published **Online**
October 3, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32329-8

See **Online/Articles**
http://dx.doi.org/10.1016/S0140-6736(18)31947-0

Hybrid closed-loop technology does not represent a cure of diabetes. It holds the promise to allow those living with diabetes to achieve more targeted glycaemic control, thereby reducing the risk of long-term complications. Furthermore, the suspension of insulin delivery feasible with these systems minimises the risk of hypoglycaemia, fear of which might lead both patients, and providers, to settle for safety with permissive hyperglycaemia. The present work provides the gold standard of a randomised trial done across the age spectrum in those with glycaemic control that is more representative of what is encountered in clinical practice. It lays the framework for patients and providers, as well as regulators and insurers, to understand the true scope of who could benefit from such systems, allowing the circle of those considered reasonable candidates for such technologies to be enlarged.

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AG has received research support from Dexcom. JLS serves as a consultant to Medtronic Diabetes, is on advisory boards for Bigfoot Biomedical, Eli Lilly, and Insulet, and has received research support from Medtronic and Insulet.

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