Next generation in insulin pump technology: The bionic pancreas?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we consider the feasibility of insulin–glucagon pumps.

Outpatient glycemic control with a bionic pancreas in type 1 diabetes.

Russell SJ, El-Khatib FH, Sinha M et al (2014) *N Engl J Med* **371**: 313–25

N Engl J Med

The bionic pancreas: Does it improve glycaemic control?

1 The aim of the studies was to compare the glycaemic control of a wearable, bihormonal, automated, "bionic" pancreas with an insulin pump in an outpatient setting in adults and adolescents with T1D over a 5-day period.

2 In two random-order, crossover studies, 20 adults and 32 adolescents took part.

3 The bionic pancreas administered insulin and glucagon with the use of algorithms housed in a smartphone and data from continuous glucose monitoring (CGM).

4 The user interface displayed the CGM tracing and insulin and glucagon doses, and users inputed details on the size of each meal and whether it was breakfast, lunch or dinner (no carbohydrate counting was required).

5 The system was initialised using only the participants' weight. No other medical history information was required.

6 The prespecified co-primary outcomes for the adult and adolescent studies were the mean plasma glucose level and the mean percentage of time during which the participant had a low glucose level (<70 mg/dL [3.9 mmol/L]).

7 Among the adults, after 1 day of automatic adaptation by the bionic pancreas, the mean (±SD) glucose level was lower than the mean level during the control period (133±13 vs 159±30 mg/dL [7.4±0.7 vs 8.8±1.7 mmol/L]; $P<0.001$) and the percentage of time with a low glucose reading was lower (4.1% vs 7.3%; $P=0.01$).

8 Among the adolescents, the mean plasma glucose level was also lower during the bionic pancreas period than during the control period (138±18 vs 157±27 mg/dL [7.7±1.0 vs 8.7±1.5 mmol/L]; $P=0.004$), but the percentage of time with a low plasma glucose reading was similar during the two periods (6.1% and 7.6%, respectively; $P=0.23$).

9 There were no episodes of severe hypoglycaemia in the adult or adolescent studies, and the mean frequency of interventions for hypoglycaemia among the adolescents was lower during the bionic pancreas period than during the control period (one per 1.6 days vs one per 0.8 days; $P<0.001$).

10 In summary, a wearable, automated, bihormonal, bionic pancreas improved mean glycaemic levels, with less frequent hypoglycaemic episodes, among both adults and adolescents with T1D.

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For older readers, the word bionic will invoke memories of Steve Austin, the *Six Million Dollar Man* from the popular 1970s TV series. Used correctly, bionic describes the application of biological principles to the design of technology, although in Austin's case, the performance of his bionic implants considerably exceeded any feasible biological system! What, therefore, is meant by a bionic pancreas?

Closed-loop insulin pump technology usually consists of continuous subcutaneous insulin infusion with a control algorithm altering insulin delivery according to continuous glucose monitoring (CGM). The challenge is that insulin can only change blood glucose levels in one direction. As an analogy, this is like driving a motor car using the accelerator but not the brake pedal. There are scenarios when insulin delivery is zero and yet blood glucose still falls (e.g. during or after exercise).

Bihormonal systems, as described in this paper, use an additional pump delivering glucagon, usually in "micro-doses" as needed, analogous to depressing the brake pedal intermittently while driving. In principle, this is a logical (and "bionic") development for closed-loop

technology, restoring glucagon responses to hypoglycaemia that are usually absent in type 1 diabetes.

Pumping two hormones is more complex than pumping one, however. A major challenge (although one that is surely solvable) is that there is currently no stable preparation of glucagon in solution. In this article, glucagon solutions were changed every 24 hours. The "brake pedal" was applied more heavily in this work, with total doses of glucagon being more than in earlier studies. Some participants exceeded 1 mg daily (equivalent to an injected emergency dose of glucagon), perhaps with implications for hepatic glycogen balance and turnover. Bihormonal systems *per se* will not overcome other challenges of closed-loop systems (e.g. accuracy of CGM and speed of onset and offset of insulin, and indeed glucagon) delivered systemically rather than portally.

On balance, though, assuming that a stable preparation of glucagon in solution can be developed, there are no major technical barriers to adding glucagon into closed-loop systems. To borrow unashamedly from the narrative in the opening credits of the *Six Million Dollar Man*, "…we have the technology"! ■

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Hype or hope? This is the question I had at the back of my mind when reading the present paper.

Glucose is lowered by insulin. That's the easy part. What is not so easy is simultaneously reducing hypoglycaemia. Russell et al achieved that in adults by aggressively co-administering insulin and glucagon in a closed-loop fashion. The extent of improvement is remarkable but not without costs.

To compensate for delays associated with subcutaneous delivery, insulin was delivered copiously so that total daily insulin administration increased by 30%, reducing mean glucose levels by 1.4 mmol/L. Excess insulin was offset by glucagon at 0.8 mg per day, three times above the amount used by the authors in their previous studies and nearly matching a 1-mg glucagon rescue dose. Plasma glucagon levels were raised, at two- to three-fold above normal fasting levels.

Apart from increasing insulin resistance, chronic hyperglucagonaemia is associated with necrolytic migratory erythema, depression and deep vein thrombosis. Long-term studies are needed to assess consequences of above-normal glucagon systemically and locally in the subcutaneous tissue. Extra insulin may induce weight gain, which may be exacerbated by a day-in, day-out liver glycogen turnover in excess of 50 g of carbohydrates (equivalent). In comparison, research into insulin-only closed-loop therapy has shown that glucose can be lowered without increasing total daily insulin, owing to a sparing effect of less aggressive insulin delivery and, possibly, increased insulin sensitivity at lower glucose levels (Leelarathna et al, 2014).

Questions arise about the true benefit of bihormonal closed-loop treatment, given that, for this analysis, greater attention was given to diabetes and device problems during the closed-loop period, when adults spent the day followed by a nurse, stayed in a hotel at night under close supervision, and probably did not work or engage in their normal daily duties, whereas during the control period they were at home or in work environments with a more demanding daily schedule and responsibilities. Would it be safe if the nurse was not around to resolve occluded or interrupted glucagon delivery, which will inevitably occur? The use of glucagon as an integral part of a control strategy to offset deliberately stacked insulin, rather than as a safety mitigation, may backfire.

Other aspects requiring resolution before considering the use of such devices in clinical practice include dual-chamber pumps and room-temperature stable glucagon. A combined glucagon–insulin cannula may increase user acceptability, as otherwise two separate infusion sites are occupied.

Is this all doom and gloom? No, not really. But it is also not all plain sailing. Properly designed long-term studies allowing evaluations during free living conditions are needed to assess the benefits and risks of aggressive co-delivery of insulin and glucagon in comparison to insulin-only closed-loop systems and conventional pump therapy.

The present study raised hopes but was unable to address these important questions. Let's hope the landing is safe, at all times. ■

Leelarathna L, Dellweg S, Mader JK et al (2014) Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. *Diabetes Care* **37**: 1931–7