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EDITORIALS

Closed loop systems in type 1 diabetes

A promising development, now patients and policy makers need much better evidence

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People with type 1 diabetes, whose immune systems destroy their insulin producing pancreatic cells, must inject insulin to stay alive. Tight control of plasma glucose prevents or delays complications such as retinopathy and nephropathy; it also avoids hypoglycaemia, the most common adverse effect of insulin treatment, which can cause, at worst, disorientation and death.

To achieve glycaemic control, people need either multiple daily injections (including long acting basal insulin once or twice daily, plus short acting insulin with meals) or an insulin pump (continuous subcutaneous insulin infusion). They must monitor blood glucose concentrations (generally by finger pricking), and adjust their insulin doses based on blood glucose, food and alcohol intake, and physical activity.[1] They should learn to adjust insulin doses through structured education programmes such as DAFNE (dose adjustment for normal eating),[2] or similar programmes for children and adolescents.

The key to achieving good control is self-management. But that is hard, even for the best motivated and educated individuals. Most people with type 1 diabetes do not achieve good control.[3-5] Technological help is available through continuous glucose monitoring devices and insulin pumps, including some that suspend insulin infusion when plasma glucose falls too low.

Closed loop systems, which are reviewed in a linked article by Bekiari and colleagues (doi:10.1136/bmj.k1310),[6] link continuous glucose monitoring and an insulin pump to a microprocessor, which uses mathematical algorithms to adjust the infusion rate. Systems can have a pump that infuses insulin alone, or a dual pump that can also infuse glucagon, a pancreatic hormone that increases blood glucose if plasma glucose falls too low. In their recent non-systematic review, Peters and Haidar[7] argue that dual systems are better than insulin pumps with the low glucose suspend facility during hypoglycaemic episodes, because glucagon restores normoglycaemia faster than stopping insulin.

Closed loop systems have four components: the pump, a continuous glucose monitoring system, the decision making microprocessor, and a system that adjusts infusion rate. The microprocessor replaces human decision making, and makes more frequent dose adjustments than a person could. Closed loop systems may reduce the stress involved in self-managing diabetes.

Bekiari and colleagues[6] systematically reviewed randomised trials of these systems, and concluded that people using them spent about 10% more time near normoglycaemia than controls using other insulin treatments. However, the overall evidence base is weak. Many trials in the review were of low quality. Type 1 diabetes is lifelong, but most trials are short—of 41 trials included, 30 lasted seven days or less. In 16 trials, the closed loop system controlled blood glucose only overnight. Of 25 trials that evaluated closed loop systems over 24 hours, only one[8] was long enough to measure glycated haemoglobin (HbA1c), which fell by only a clinically insignificant 0.3% (3.3 mmol/mol) after 12 weeks. Severe hypoglycaemia was too infrequent for meaningful comparisons. Many trials did not use continous glucose monitoring in the control arms. Bekiari and colleagues did not consider the effect of treatment type on quality of life.

None of the 17 trials in children or adolescents included children younger than 5 years, a group in which closed loop technology might reduce parental anxiety about nocturnal hypoglycaemia. Older children might benefit from increased independence and more participation in activities that otherwise need substantial adult oversight.

What does this new review mean for people with type 1 diabetes, and policy makers? Closed loop systems can improve control overnight, and reduce the burden of self-management during the day by reducing frequent decisions on adjustments to insulin dose. However, we do not know whether these systems reduce the long term complications of diabetes. For policy makers, there are insufficient data for cost effectiveness analysis.

We need longer and larger trials, in both adults and children, to compare closed loop systems with self-management using continuous glucose monitoring. These trials should measure

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HbA1c (for modelling the effects on complications), blood glucose variability, hypoglycaemia, quality of life, and cost effectiveness. Patients with particular problems, such as hypoglycaemia without warning symptoms, could benefit more. For children, we need data on parents' quality of life. We need a trial of the dual insulin and glucagon system in cystic fibrosis related diabetes, where pancreatic and hepatic damage impairs responses to both hypoglycaemia and hyperglycaemia.

Manufacturers need not look for complete automation. People with type 1 diabetes will remain involved in management. But closed loop systems, as well as open loop systems with data acted on by the user, could reduce the burden.

Future research can benefit from the experience of the community of users and patient technology developers,[9] through initiatives such as the OpenAPS network,[10] with over 1.4 million hours of closed loop experience according to a 2017 TED talk (https://www.youtube.com/watch?v=_J47aqiTrtc).

Closed loop systems have much to offer, but we need better evidence to convince policy makers faced with increasing demands and scarce resources.

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