Nocturnal hypoglycaemia after exercise: Can it be avoided with closed-loop pump technology?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we focus on a the effect of using the closed-loop glucose monitoring system in eliminating nocturnal hypoglycaemia in young people with type 1 diabetes after exercise.

Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes.

Sherr JL, Cengiz E, Palerm CC et al (2013) *Diabetes Care* **36**: 2909–14

DIABETES CARE

Closed-loop pumps reduce the risk of nocturnal hypoglycaemia

1 This randomised crossover study compared the use of open-loop (OL) and closed-loop (CL) glucose monitoring systems in preventing nocturnal hypoglycaemia (NH) after antecedent afternoon exercise.

2 Twelve young people (aged 16.8 ± 3.6 years) with well-controlled T1D participated. Participants used both OL and CL insulin delivery on two separate 48-hour inpatient stays, and both consisted of an exercise protocol for 24 hours, and a sedentary protocol for 24 hours.

3 The exercise protocol was carried out at 1500 to mimic "after-school" exercise and was the 75 minute, vigorous procedure from the DirecNet study (four 15-minute exercise periods with three 5-minute rest periods inbetween).

4 Throughout the study, hypoglycaemia was defined as a reference blood glucose of <70 mg/dL (<3.9 mmol/L), and the target range was defined as 70–180 mg/dL (<3.9–10.0 mmol/L).

5 There was no significant difference in overall 24-hour mean blood glucose levels between OL and CL delivery once blood glucose levels <70 mg/dL were removed from the analyses.

6 On sedentary days, CL delivery significantly lowered overnight blood glucose compared to OL delivery (98% versus 87% of values within the target range respectively; $P<0.0001$).

7 When exercise occurred during the OL protocol, the risk of low glucose levels increased to 11%; during the CL protocol, glucose control was maintained.

8 When the sedentary and exercise days were combined, there were significantly more episodes of treatable NH during CL delivery than OL delivery ($P=0.04$).

9 Less insulin was administered between 2200 and 0200 in the CL compared to the OL on days after exercise ($P=0.008$).

10 CL insulin delivery reduced the risk of NH and increased the time spent in the target blood glucose range regardless of whether exercise took place or not ($P=0.23$). However, the CL system did not fully eliminate NH on exercise or sedentary days.

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Helen Partridge, Consultant Diabetes and Endocrinology, Royal Bournemouth Hospital

Fear of hypoglycaemia remains the greatest barrier to exercise in people with type 1 diabetes, with up to 48% of children with type 1 diabetes experiencing nocturnal hypoglycaemia (NH) after a single bout of daytime exercise. Significant NH, *per se*, is a huge and dangerous problem, and one which can then attenuate the counter regulatory response to exercise in the subsequent 24 hours. Multiple potential strategies, particularly insulin pump therapy, exist to reduce the frequency of NH, but none yet have provided a panacea because of the panoply of variables at play.

Closed-loop systems are progressing at a tremendous rate, and there is now data on some of the first outpatient trials to assess safety and efficacy with very exciting results (Kovatchev et al, 2013). Integration of this technology into the management plans of people keen to exercise holds great promise, and this study by Jennifer Sherr et al gives us some early insight into its potential benefits.

As with all new technologies, safety and efficacy have to be at the forefront. Evidence is accumulating on the reliability of continuous glucose monitoring systems during exercise, but there are concerns over the calibration of such systems during times of rapid glucose change (Kumareswaran et al, 2013). Multiple neurohormonal factors predisposing to NH are at play both during and after exercise. Counter regulatory hormones increase during exercise, particularly during high intensity and anaerobic exercise, with a hang-over effect lasting up to around 12 hours. With the increased insulin sensitivity over this same time frame, the propensity to develop hypoglycaemia over this period is very high, and these large glucose fluctuations may influence the reliability of interstitial glucose sensing. This proof of concept study by Sherr et al has provided some reassuring evidence on both safety and reliability in this situation, albeit in an in-patient setting of young people with reasonably good overall control.

At this current time, clinical application of these systems is still restricted by concerns over system failures and inappropriate insulin delivery and, therefore, most studies remain restricted to small, in-patient groups.

Translation of this technology into routine clinical practice, whilst a very alluring prospect, is still some way off and, certainly in the UK, would be further restricted by funding processes. However, closed-loop systems are very exciting, and this study adds to the growing evidence of safety and reliability, which is particularly enticing when exercise is thrown into the milieu.

Kovatchev BP, Renard E, Cobelli C et al (2013) Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. *Diabetes Care* **36**: 1851–8

Kumareswaran K, Elleri D, Allen JM et al (2013) Accuracy of continuous glucose monitoring during exercise in type 1 diabetes pregnancy. *Diabetes Technol Ther* **15**: 223–9

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The development of an autonomous closed loop system for glucose control would be one the most significant advances in type 1 diabetes treatment since the discovery of insulin over 90 years ago. While further development and optimisation is required, the technology utilised in this paper brings this ambition closer to reality, and confirms that it is possible to improve overnight glycaemic control following exercise.

The challenge of controlling blood glucose for individuals with type 1 diabetes is further exacerbated when exercise is performed for leisure or competitive purposes. Insulin and exercise exert similar effects on glucose uptake, but differ in the mechanism and duration of action. Despite the health-related benefits of exercise, the complexity of matching the "insulin–exercise–glucose" interdependencies for people with type 1 diabetes, coupled with the risk of hypoglycaemia for up to 16 hours post exercise, makes glycaemic control a real challenge. The task is not easy for clinicians either, as the high inter-individual variability to exercise makes it difficult to provide support and recommendations.

Some individuals with type 1 diabetes who exercise regularly, especially for participation in sport, tend to run high blood glucose levels. This is the result of nutrition strategies and altered insulin regimes to avoid hypoglycaemia, rather than meeting the energy demands of exercise. There is a concern that some individuals may conceal or downplay their diabetes to avoid the attention, or potential worry, of coaches, teachers and other players who would have to deal with their hypoglycaemia.

Therefore, the further development of this technology will be significant for those people with type 1 diabetes who exercise, and their clinicians. It has the potential to obviate the need for compensatory strategies to avoid hypoglycaemia, to increase the confidence of the individual and, in the longer term, to help to improve glycaemic control and reduce the risk of complications.