THE LANCET
Diabetes & Endocrinology

Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

Table 1a

Automated handling of exercise	
Considerations	Current commercially available closed-loop systems may facilitate improved glucose control during and exercise, but hypoglycemia can still occur[1-3]
	All systems allow higher glucose targets for exercise: • These should be initiated 60-90 minutes before exercise onset to allow the levels of circulating insulin to decrease[4] • Typically, still requires small amounts of carbohydrate (~15-30g), either just before the exercise starts, or if the glucose falls below 7.0 mmol/L during the activity[5]
	All forms of prolonged exercise can result in increased hypoglycemia risk over the next 6-12 hours and higher glucose targets may be needed in recovery[6]
User actions required	For exercise within two hours of a meal, a 25-75% reduction in bolus insulin is recommended for insulin-only closed-loop systems[4]
	Typically, only aerobic and mixed forms of physical activity lasting >30 min require higher glucose targets and reduced closed-loop insulin delivery
	More intense or brief forms of anaerobic exercise may require insulin administration for avoidance of post-exercise hyperglycemia[7]
Future work	Physiologic models of various exercise types and intensities[8] could inform an unannounced exercise-aware model predictive controller for better handling of hormone delivery around exercise[9]
	Additional inputs may better inform exercise management (e.g., physical activity wearables, lactate, ketones)
	User specific factors (sex, muscle/fat mass, fitness levels, individual goals such as weight loss/improved performance etc.) will need to be considered

Table 1b

Multihormone closed-loop systems	
Glucagon	
Pros	Reduce exercise-induced and insulin-induced hypoglycemia while maintaining glucose time in range.[10,11]
Cons	Increased system complexity and cost
	Nausea and vomiting
	Hypoglycemia - if glucagon is called for and infusion set failure occurs
	Hyperglycemia or diabetic ketoacidosis (DKA) - if glucagon is delivered in response to an inaccurate low CGM reading
Future work	Dosing strategies to reduce gastrointestinal side effects (titration up over time, micro dosing, continuous infusion)
	Evaluation for changes in insulin dose requirements with various glucagon dosing strategies
	Need for long term human trials for assessment of overall safety and potential immunogenicity of glucagon analogs
	Need for studies on stability and feasibility in pumps
Pramlintide	
Pros	Reduces glucose excursions after a meal[12] by slowing gastric emptying[13] and inhibiting endogenous post-meal glucagon release[14]
	Opportunity for a fully automated closed-loop system by combining automated meal detection, ultra-fast acting insulin analogs and pramlintide for superior daytime glucose control[15]
Cons	Nausea and vomiting
	Post-meal hypoglycemia can occur
Future work	Fixed ratio co-formulation pramlintide/insulin may soon be available[16]
	Dosing strategies to reduce gastrointestinal side effects (titration up over time, micro dosing, continuous infusion)
	Need for studies on stability and feasibility in pumps

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