Project Details	
Project Code	CMD27Ex Podlogar
Title	Metabolic adaptation to a low carbohydrate ketogenic diet and its effects on exercise fuel use and glucose management in physically active people with Type 1 Diabetes
Research Theme	Cardiometabolic Disease
Project Type	Wet lab
Summary	Ketogenic diet (very low in carbohydrate, high in fat) is increasingly popular among people with Type 1 Diabetes (T1D). In principle, a ketogenic diet could benefit T1D. By relying more on fat for fuel, the body may need less insulin and experience more stable blood glucose, potentially making exercise safer and easier to manage. But nobody has tested what actually happens to fuel use and glucose control during exercise in physically active people with T1D on this diet. This project will be the first to find out, providing evidence to support safer, personalised dietary guidance for T1D population.
Description	Background Type 1 diabetes (T1D) is an autoimmune condition characterised by progressive loss of pancreatic beta cells, resulting in lifelong dependence on exogenous insulin. Physically active people living with T1D face a complex management challenge: exercise alters glucose flux, and the interaction between exercise intensity, circulating insulin and carbohydrate availability creates a narrow therapeutic window for blood glucose stability. Fear of hypoglycaemia is consistently identified as a major barrier to physical activity in this population, with consequences for long-term cardiometabolic health. Ketogenic diets (KD; typically <50 g carbohydrate per day) are increasingly popular and widely self-adopted within the T1D community, often outside clinical oversight. An international survey of adults with T1D following a very low-carbohydrate diet reported excellent glycaemic control and low rates of acute adverse events, highlighting both the scale of self-adoption and the need for controlled trials to establish safety, efficacy and generalisability. There is a strong mechanistic rationale for potential benefit: by shifting fuel use toward fat oxidation and ketone body production, a KD may reduce and stabilise insulin requirements, widening the margin of safety around exercise where unpredictable insulin action is a principal driver of hypoglycaemia risk. No study has investigated physically active adults with T1D using hybrid closed-loop insulin delivery who undertake a KD, nor directly characterised exercise fuel metabolism or exogenous carbohydrate needs in this setting. A parallel-group RCT in healthy adults using detailed metabolic phenotyping including muscle biopsy, in which a member of the present supervisory team was a senior author, provides methodological precedent but has not been extended to T1D or exercise-specific outcomes. A recent literature review concluded that metabolic responses to low-carbohydrate diets during exercise in T1D remain essentially unexplored. Carbohydrate ingestion during exercise is standard practice to prevent hypoglycaemia in T1D, yet whether exogenous carbohydrate requirements change after KD adaptation is unknown. Under ketogenic conditions hepatic glycogen stores are low, raising the possibility that

	exogenous carbohydrate reliance during exercise may increase, that generic guidance may under-dose this group, and that recovery from hypoglycaemia during remote or unsupervised exercise could be impaired - particularly important given that hypoglycaemia fear already limits activity in T1D. No study has quantified exogenous carbohydrate oxidation or defined practical dosing requirements in physically active people with T1D following a KD. Primary Research Question How does a six-week ketogenic diet alter metabolic adaptation, skeletal muscle phenotype and fuel use during exercise - including exogenous carbohydrate requirements - in physically active adults with T1D using hybrid closed-loop insulin delivery? Secondary Research Questions How does a KD affect glycaemic control measured by standard CGM parameters? How does it influence subjective wellbeing? How acceptable and sustainable do participants find a KD combined with regular exercise and closed-loop therapy? Study Design We will conduct a parallel-group RCT in approximately 15-20 physically active adults with T1D per group, randomised to a KD or control diet for six weeks using hybrid closed-loop insulin delivery, followed by structured endpoint testing. All KD participants will receive dietician-led education and support, and the study will fully fund adherence costs including specialist foods and ketone monitoring supplies. The parallel-group design is preferred over a crossover because KD-induced adaptations are unlikely to wash out within a feasible interval and repeating prolonged dietary periods with invasive testing would substantially increase burden and attrition. Objectives and Measurements Objective 1 - Time course of metabolic adaptation: CGM and pump data will be collected continuously, providing records of time in range, glycaemic variability, hypoglycaemia episodes and total daily insulin dose. Participants will maintain a training diary. Fasting blood samples at baseline, week 3 and week 6 will measure glucose, ketone bodies, NEFA, lipid profile and HbA1c. Objective 2 - Exercise fuel use and exogenous carbohydrate requirements: Standardised maximal and submaximal cycling tests at baseline and six weeks will allow within-person and between-group comparison. The submaximal test will be performed twice at endpoint: without exogenous carbohydrate to characterise endogenous substrate utilisation, and with ingested ^{13}C-labelled glucose to quantify exogenous glucose oxidation. Indirect calorimetry will measure substrate oxidation throughout; blood samples will measure glucose, lactate, ketone bodies, NEFA, insulin and glucagon. Objective 3 - Skeletal muscle phenotype: Muscle biopsies in a defined participant subset will be analysed for markers of metabolic adaptation, providing mechanistic insight into the exercise and CGM findings. Objective 4 - Wellbeing, hypoglycaemia awareness and acceptability: Validated questionnaires at baseline and six weeks will assess quality of life, wellbeing, hypoglycaemia awareness and cognitive function. Post-intervention semi-structured interviews will explore experiences of

	following a KD with closed-loop therapy and regular exercise, perceived benefits and harms, and views on sustainability. Student Ownership The exact balance of the protocol will be determined collaboratively with the student during the Prep period, based on their interests and skills, with scope to extend toward sex-specific analyses or additional mechanistic measures if recruitment and timelines allow.
Can be completed part time?	Yes
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