# SUMMARY (Clinical) 6/3/25 ciT1zen science

## Prebiotic supplementation in patients with type 1 diabetes: study protocol for a randomised controlled trial in Canada ciT1zen science summary

**Source:** Huang C, Rosolowsky E, Nour MA, et al. Prebiotic supplementation in patients with type 1 diabetes: study protocol for a randomised controlled trial in Canada. BMJ Open 2025;15:e102486. doi: 10.1136/bmjopen-2025-102486

**Date:** [Insert Date]

**Subject:** Review of a randomized controlled trial protocol investigating prebiotic supplementation as an adjunctive therapy for Type 1 Diabetes (T1D) in Canada.

**Summary:** This document outlines the protocol for a multicentre, randomised, double-blind, placebo-controlled study to investigate the effects of prebiotic supplementation (oligofructose-enriched inulin) on various health outcomes in individuals with Type 1 Diabetes (T1D). The study hypothesizes that prebiotic supplementation, used as an adjunct to insulin therapy, will reduce the frequency of hypoglycaemia, improve glycaemic variability, enhance serum C peptide levels (a marker of residual beta-cell function), reduce intestinal permeability (IP) and systemic inflammation, and alter gut microbiota composition and function. The study builds upon previous pilot data suggesting that prebiotics can preserve C peptide levels and reduce hypoglycaemia in children with T1D.

**Key Themes and Ideas:**

1. **Type 1 Diabetes Management Challenges:** The source highlights the significant disease burden of T1D, including the need for multiple daily interventions, meticulous monitoring, and the constant risk of complications such as hypoglycaemia, ketoacidosis, and long-term vascular issues. Existing adjunctive therapies have limitations in efficacy and safety, particularly in children. The study emphasizes the need for novel, low-risk approaches, positioning nutritional therapy, specifically prebiotic supplementation, as a promising area of investigation.

- "Despite treatment advances, patients still face increased mortality and serious complications, including hypoglycaemia, ketoacidosis, blindness, amputation, cardiovascular disease and kidney failure."
- "Although several adjunctive therapies aimed at improving glycaemic control in T1D have been tested... efficacy has yet to be proven in children, and there are concerns about potentially serious side effects and high cost."

1. **The Role of Gut Microbiota and Intestinal Permeability in T1D:** The protocol emphasizes the "compelling evidence that an abnormal gut microbiota or dysbiosis can increase intestinal permeability (IP) and contribute to dysglycaemia seen in T1D." Increased IP ("gut leakiness") allows harmful substances to enter the bloodstream, contributing to inflammation, immune activation, and potentially beta-cell destruction.

- "Compelling evidence links abnormal gut microbiota or ‘dysbiosis’ to increased ‘gut leakiness’ and T1D."
- "Increased IP allows environmental antigens and bacterial endotoxins to cross intestinal mucosa and enter the systemic circulation, causing immune activation, contributing to beta-cell destruction and reduced C peptide."

1. **Prebiotics as a Potential Intervention:** Prebiotics are defined as "substrates selectively used by host microorganisms to confer a health benefit." The study focuses on inulin-type fructans, specifically oligofructose-enriched inulin, which has shown promise in previous studies (in rodents, adults, and

children) for improving various metabolic parameters and increasing beneficial gut bacteria like *Bifidobacterium*.

- "Prebiotics are substrates selectively used by host microorganisms to confer a health benefit."
- "We have shown in rodents, adults and children with overweight or obesity that prebiotics, specifically inulin-type fructans... can... improve glycaemia and increase the abundance of gut bacteria that are metabolically beneficial to the host (eg, *Bifidobacterium*)."

1. **Pilot Study Findings:** The protocol references a prior pilot study that demonstrated several key positive effects of prebiotic supplementation in children with T1D:

- **Reduced Hypoglycaemia:** A significant reduction in the frequency of hypoglycaemic events was observed in the prebiotic group compared to placebo.
- **Preserved C Peptide Levels:** The prebiotic group maintained their serum C peptide levels, a marker of residual insulin-producing beta-cell function, while the placebo group showed a drop. This is clinically significant as preserved C peptide is associated with less glucose fluctuation, better glycaemic control, and lower risk of complications.
- **Trend towards Improved Intestinal Permeability:** The prebiotic group showed a trend towards decreased IP.
- **Alterations in Gut Microbiota:** An increase in *Bifidobacterium* was observed in the prebiotic group, and a negative correlation was found between serum C peptide and the abundance of *Terrisporobacter* (linked to inflammation).
- "In a pilot study, we showed that in children who had T1D for at least 1 year, a 3-month course of prebiotic fibre significantly reduced the frequency of hypoglycaemia."
- "Importantly, the prebiotic group maintained their serum C peptide level (marker of residual beta cell function) while the placebo group saw a drop."

1. **Hypothesis and Primary Objective:** The core hypothesis is that prebiotic supplementation will improve glycaemic control, specifically by reducing hypoglycaemia and glycaemic variability, mediated by improved C peptide levels, reduced IP and inflammation, and positive changes in the gut microbiome. The primary objective is to confirm the reduction in hypoglycaemia frequency with prebiotic supplementation over a 6-month period.

- **Hypothesis:** "We hypothesise that, as an adjunct to insulin, prebiotic supplementation will reduce the frequency of hypoglycaemia and improve glycaemic variability that is accompanied by enhanced serum C peptide levels, a reduction in IP and systemic inflammation and altered gut microbiota."
- **Primary Objective:** "The primary objective of this trial is to compare the change in frequency of hypoglycaemia from baseline to 6 months in individuals with T1D treated with a 6-month course of prebiotic or placebo as an adjunct to insulin."

1. **Study Design and Methodology:** The study is designed as a robust, multicentre, randomized, double-blind, placebo-controlled trial involving 144 participants aged 7 and above with T1D across three Canadian sites.

- **Randomization:** Participants will be randomized 1:1 to either the prebiotic (oligofructose-enriched inulin) or placebo (isocaloric maltodextrin) group. Stratification will be by sex and age group (7–17 years or ≥18 years).
- **Blinding:** Participants, study staff, and those performing analysis will be blinded to the intervention.
- **Intervention:** A 6-month intervention period with daily consumption of the assigned supplement. Doses will be titrated up over 2 weeks (8g/day for 7-13 years, 16g/day for ≥14 years).
- **Duration:** 6 months of intervention with follow-up at 9 months to assess persistence of effects.

1. **Outcome Measures:** A comprehensive set of primary and secondary outcomes will be assessed:

- **Primary Outcome:** Frequency of hypoglycaemia (measured by CGM and blood glucose logs).
- **Secondary Outcomes:**Glycaemic variability and control (CGM metrics: TIR, TBR, TAR; and A1C).
- Stimulated C peptide and pro-insulin levels.
- Intestinal permeability (lactulose/mannitol ratio, serum LPS).
- Serum inflammatory markers (IL-6, IFN-γ, TNF, CRP, IL-10).
- Quality of life (QOL) and fear of hypoglycaemia ratings.
- Adverse reactions (severe hypoglycaemia, DKA, side effects).
- Gut microbiome composition and function (shotgun sequencing) and metabolites (faecal and serum metabolomics).
- Persistence of hypoglycaemia frequency and glycaemic variability/control at 9 months (3 months post-intervention).

1. **Data Collection and Analysis:** The study employs various methods for data collection, including in-person visits, virtual follow-ups, continuous glucose monitoring (CGM), blood draws, urine and faecal sample collection, questionnaires, and dietary intake assessments. Sophisticated multiomics technology (shotgun sequencing and metabolomics) will be used to investigate the mechanisms by which prebiotics exert their effects. Statistical analysis will utilize intention-to-treat principles and advanced methods to analyze clinical, microbiome, and metabolomic data.
2. **Ethical Considerations:** The study has received ethical approval from multiple boards in Canada. Written informed consent/assent will be obtained from participants/guardians. Confidentiality will be maintained through data de-identification and secure storage.
3. **Significance and Dissemination:** The study is positioned as potentially establishing prebiotic supplementation as a "low-cost, low-risk, dietary intervention that improves health outcomes in those with T1D." Results will be disseminated through peer-reviewed publications and conference presentations, with the ultimate goal of informing clinical practice guidelines. The inclusion of multiple sites and participants newly diagnosed with T1D (with potentially higher residual beta-cell function) is expected to improve the generalizability and impact of the findings.

- "Prebiotic supplementation is a low-risk intervention in those with T1D that is supported by strong preliminary data, demonstrating efficacy in preserving pancreatic beta-cell function and reducing the risk of hypoglycaemia in those with long-standing T1D."
- "Results from this study may establish prebiotic supplementation as a low-cost, low-risk, dietary intervention that improves health outcomes in those with T1D."

**Most Important Ideas/Facts:**

- Type 1 Diabetes management is complex and current adjunctive therapies have limitations.
- Abnormal gut microbiota and increased intestinal permeability are linked to T1D and dysglycaemia.
- Prebiotic fibre has shown potential to mitigate dysbiosis, reduce IP, and improve glycaemic control.
- A pilot study showed that prebiotic supplementation in children with T1D significantly reduced hypoglycaemia frequency and preserved C peptide levels.
- Preserving C peptide levels is crucial for better glycaemic control and reduced risk of hypoglycaemia and complications.
- The current study is a large-scale, multicentre, randomized, double-blind, placebo-controlled trial aiming to confirm and expand upon the pilot findings.
- The study will assess a wide range of outcomes, including hypoglycaemia, glycaemic variability, C peptide, intestinal permeability, inflammation, and gut microbiome changes.
- The trial aims to determine if prebiotic supplementation can serve as a safe, effective, and low-cost adjunctive therapy for T1D, particularly by preserving beta-cell function and reducing hypoglycaemia.

**Conclusion:**

This study protocol outlines a well-designed trial to rigorously evaluate the potential benefits of prebiotic supplementation in individuals with Type 1 Diabetes. Building on promising pilot data, the study's comprehensive approach, including multiomics analysis, has the potential to provide valuable insights into the role of the gut microbiome in T1D and establish a novel dietary intervention to improve glycaemic control and reduce the significant burden of this chronic disease.