Fecal Microbiota Transplantation for The Early-Onset Type 1 Diabetes. Could It Be a Promising Solution?

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Abstract from de Groot P, Nikolic T, Pellegrini S, et al.: Faecal microbiota transplantation halts progression of human new-onset type 1 diabetes in a randomised controlled trial. Gut. 2021;70(1):92–105.

Keywords
Diabetes mellitus

Objective: Type 1 diabetes (T1D) is characterised by islet autoimmunity and beta cell destruction. A gut microbiota–immunological interplay is involved in the pathophysiology of T1D. We studied microbiota-mediated effects on disease progression in patients with type 1 diabetes using faecal microbiota transplantation (FMT).

Design: Patients with recent-onset (<6 weeks) T1D (18–30 years of age) were randomised into two groups to receive three autologous or allogenic (healthy donor) FMTs over a period of 4 months. Our primary endpoint was preservation of stimulated C peptide release assessed by mixed-meal tests during 12 months. Secondary outcome parameters were changes in glycaemic control, fasting plasma metabolites, T cell autoimmunity, small intestinal gene expression profile and intestinal microbiota composition.

Results: Stimulated C peptide levels were significantly preserved in the autologous FMT group (n = 10 subjects) compared with healthy donor FMT group (n = 10 subjects) at 12 months. Small intestinal Prevotella was inversely related to residual beta cell function (r = −0.55, p = 0.02), whereas plasma metabolites 1-arachidonoyl-GPC and 1-myristoyl-2-arachidonoyl-GPC levels linearly correlated with residual beta cell preservation (rho = 0.56, p = 0.01 and rho = 0.46, p = 0.042, respectively). Finally, baseline CD4+CXCR3+T cell counts, levels of small intestinal Desulfovibrio piger and CCL22 and CCL5 gene expression in duodenal biopsies predicted preserved beta cell function following FMT irrespective of donor characteristics.

Conclusion: FMT halts decline in endogenous insulin production in recently diagnosed patients with T1D in 12 months after disease onset. Several microbiota-derived plasma metabolites and bacterial strains were linked to preserved residual beta cell function. This study provides insight into the role of the intestinal gut microbiome in T1D.

Trial registration number: NTR3697.
Knowledge Transfer

**Background**
Type 1 diabetes mellitus (T1D) is an autoimmune disease whose pathophysiology recently has been linked with intestinal dysbiosis. Preclinical studies in non-obese diabetic (NOD) mice showed that interaction between commensal flora and the innate immune system is the cornerstone for the development of T1D. It is considered that the development of T1D is related to an increased intestinal permeability, induced by an impaired intestinal short-chain fatty acid (SCFA) production (end products of fiber fermentation). In this framework, fecal microbiota transplantation (FMT) could be a solution in improving the small intestinal immune system.

**Study Results**
The study by de Groot P et al. [1] was published in Gut in October 2020. It was the first exploratory randomized controlled trial that highlighted the effect of FMT – autologous (their own) or allogenic (from healthy donors) – on residual beta-cell function in patients with new-onset T1D in the Amsterdam region. Lack of funding led to a limited sample size of 20 patients who underwent FMT by nasoduodenal tube at 0, 2, and 4 months. The researchers studied the differences between the two groups (N1 = 10 with autologous FMT and N2 = 10 with allogenic FMT) in fasting plasma C-peptide and HbA1c at 6 and 12 months. All patients had a normal body mass index (18.5–25 kg/m²) and were given mixed meals and similar amounts of exogenous insulin. At baseline, fasting plasma C-peptide was similar between groups. Twelve months later, C-peptide levels were preserved in the autologous FMT group but exacerbated in the allogenic FMT group (Fig. 1). Similar results were observed for residual beta-cell function as expressed by the response of stimulated C-peptide area under the curve (AUC), which was equal at baseline (p value 0.92); however, one year later after autologous FMT their function was significantly preserved (p value 0.033). Glycaemic control as expressed by HbA1c showed no significant difference between groups. HbA1c levels decreased after insulin treatment but did so in both groups (Fig. 2). Analyses of secondary endpoints included immunological assays like fluorescent-activated cell sorting, lymphocyte stimulation assays, and human leucocyte antigen multimer analyses to enumerate CD8 T cell autoimmunity to islet autoantigens (CD8 Quantum dot) at 0, 2, 6, 9, and 12 months. Furthermore, targeted plasma metabolites were measured at 0, 6, and 12 months; gastroduodenoscopy with duodenal biopsies was performed at 0 and 6 months to assess small intestinal microbiota and perform quantitative reverse transcription PCR to assess duodenal gene expression. Multiomics analysis identified a significant bacterial strain named *Desulfovibrio piger*, which was associated with a change in stimulated C-peptide responses on FMT and increased amounts in the autologous group. *D. Piger* correlated positively with levels of plasma 1-arachidonoyl-GPC, a beneficial glycerophospholipid.

Unexpectedly, autologous FMT had better results than healthy donor FMT. Researchers speculate that allogenic FMT increases the inflammatory status which is already present at the time of T1D diagnosis because donor gut microbiota is not compatible with the host. Thus, foreign microbiota is less tolerated by the immune system and specifically by T cells which are located in the epithelium of the small intestine.

**Conclusion for Clinical Practice**
This is the first time that FMT is applied in humans with recent onset of T1D. In spite of the small sample size the results are promising, showing prolonged residual beta-cell function. Increased plasma phospholipids and tryptophan derivatives (1-arachidonoyl-GPC and 1-myristoyl-2-arachidonoyl-GPC) after FMT were associated.
with beneficial changes in immune cell subsets such as CD4+ T cells. FMT could be a potential therapeutic solution due to the perception of ‘natural’ treatment and its relatively inexpensive implementation.

Disclosure Statement
I hereby confirm that there are no conflicts of interest pertaining to this commentary.

References
1. de Groot P, Nikolic T, Pellegrini S, et al.: Faecal microbiota transplantation halts the progression of human new-onset type 1 diabetes in a randomized controlled trial. Gut. 2021 Jan; 70(1): 92–105.

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