Autologous faecal microbiota transplantation for type 1 diabetes: a potential mindshift in therapeutic microbiome manipulation?

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A growing body of evidence shows that the alteration of gut microbiota is involved in the pathogenesis of both autoimmune and metabolic disorders. This connection is straightforward, as human gut microbiota is known to shape the immune system and regulate the metabolism during early life, so its imbalance is expected to breach the homoeostatic healthy state and be a potential driver of disease. Based on this background, the increasing prevalence of both autoimmune and metabolic disorders worldwide has been hypothesised to be potentially caused by the progressive depletion of human gut microbiota that are associated with modern Western lifestyle.[1] More specifically, this intriguing evolutionary theory rests on the evidence of common mechanistic pathways of response to changes in gut microbiome, that are shared by autoimmune and metabolic diseases. The use of broad-spectrum antibiotics—which are, basically, the fastest and most detrimental driver of dysbiosis—during early life has been identified as a risk factor for the later development of both early onset IBD[2] and obesity/overweight,[3] in human cohorts and in elegant mouse models.[3] On the other side, the therapeutic modulation of gut microbiota, mainly faecal microbiota transplantation (FMT), has brought promising results in these settings, including UC[4] and metabolic syndrome (MetS).[5]

Type 1 diabetes (T1D) represents an interesting disease model, as it is an autoimmune disease with relevant metabolic alterations. Several lines of evidence suggest that intestinal dysbiosis can also play a major role in the pathogenesis of T1D. The interplay between gut microbiota and the innate immune system of the host is a critical epigenetic factor for the development of T1D,[6] and antibiotics have been found to accelerate the clinical onset of the disease.[7] However, despite this pathogenic background, the therapeutic modulation of the gut microbiome has not been investigated yet as a potential treatment option for patients with T1D, as happened in UC or MetS.

In a randomised controlled trial of 21 patients with new onset T1D, de Groot and colleagues have investigated the effect of donor FMT over autologous FMT in

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preserving the mixed meal test (MMT)-stimulated C-peptide release at 6 months and 12 months compared with baseline (primary end point).[8]

Unexpectedly, autologous FMT was more effective than donor FMT in preserving the levels of MMT-stimulated C-peptide release at the end of follow-up. Irrespective of treatment groups, specific metabolic and microbial characteristics of patients at the baseline predicted clinical response. No significant differences in glycaemic control and alpha diversity of the small bowel microbiome were observed between groups at the end of treatments. Finally, no major shifts in the composition of small bowel microbiome were found. Several reasons, to be searched mainly on different details of the study, may underlie these results.

Above all, the study was interrupted before reaching the predicted sample size, because of lack of funding, so any result should be taken with caution and cannot be considered as conclusive.

Donor FMT did not perform better than autologous FMT neither on clinical nor on microbiological outcomes. This is in line with previous literature, as clinical and microbiological results go usually parallel in FMT studies.[4 5 9] In the present study, patients received three autologous or allogenic faecal infusions by nasoduodenal tube using 200–300 g of freshly produced faeces at 0, 2 and 4 months, and donors for allogenic FMT were lean healthy individuals.

Previous evidence suggests that a specific choice of donors[5] and a high quantity of faeces[10] are associated with clinical success in FMT studies. Also the use of multiple faecal infusions is commonly known to promote both microbial engraftment and clinical success better than single FMT.[4 5 10 11]

However, in the present study infusions were separated by a long time frame (2 months), and this choice could have influenced results. As shown in patients with UC, the application of intensive and/or condensed infusion protocols[4 11] was associated with positive findings, and can be considered a favourable approach for clinical success, at least when investigating FMT in chronic disorders.

Moreover, the primary end point was assessed at 12 months after the start of treatments, so 6 months after the last faecal infusion. Available data from studies in MetS suggest that clinical benefits of FMT get lost, together with donor microbial engraftment, in the midterm after transplant,[5] and most of the successful FMT studies,[4 5 9 10] irrespective of disease, have chosen a much shorter follow-up to assess the primary end point, compared with the present study.

Another detail could rely in the duodenal infusion: this approach is surely interesting, as it is expected that host-microbial interplays that could influence T1D outcomes occur mainly at the small bowel level. However, gut microbiota is much more abundant in the large bowel rather than in the small bowel, so even the pathways of interaction with the host are increased. Additionally, most of the data on the immune properties of the gut microbiome come from the assessment of faecal microbiome. *Akkermansia muciniphila*, a deep anaerobe living mostly in the large bowel, is well known to have immune and metabolic advantages, and has recently shown favourable effects in a model of non-obese diabetic mice.[12] Finally, as suggested by the authors, immunological benefits of FMT could happen when the infused microbiome is immunologically closer to the host, and that the small intestine of the host could have been less tolerant to allogenic microbiome. So, the simple transfer of autologous faecal microbiome into a different environment, as the duodenum is, could have beneficial effects, while the transplant of donor stool in the small bowel, despite promising results in purely metabolic patients,[5] could have increased intestinal permeability, which is known to play a key role in T1D and autoimmune disorders.

In conclusion, even if results are not clinically positive, this pioneer study remarks that the accurate choice of protocol details is critical for FMT success, and, more importantly, its findings pave the way for including autologous FMT among our approaches to therapeutic microbiome manipulation.

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REFERENCES

1 Blaser MJ. The theory of disappearing microbiota and the epidemics of chronic diseases. *Nat Rev Immunol* 2017;17:461–3.
2 Örtqvist AK, Lundholm C, Halfvarson J, *et al*. Fetal and early life antibiotics exposure and very early onset inflammatory bowel disease: a population-based study. *Gut* 2019;68:218–25.
3 Cox LM, Blaser MJ. Antibiotics in early life and obesity. *Nat Rev Endocrinol* 2015;11:182–90.
4 Costello SP, Hughes PA, Waters O, *et al*. Effect of fecal microbiota transplantation on 8-Week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA* 2019;321:156–64.
5 Kootte RS, Levin E, Salojärvi J, *et al*. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. *Cell Metab* 2017;26:611–9.
6 Wen L, Ley RE, Volchkov PY, *et al*. Innate immunity and intestinal microbiota in the development of type 1 diabetes. *Nature* 2008;455:1109–13.
7 Livanos AE, Greiner TU, Vangay P, *et al*. Antibiotic-mediated gut microbiome perturbation accelerates development of type 1 diabetes in mice. *Nat Microbiol* 2016;1:16140.
8 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;70:92–105.
9 Ianiro G, Rossi E, Thomas AM, *et al*. Faecal microbiota transplantation for the treatment of diarrhoea induced by tyrosine-kinase inhibitors in patients with metastatic renal cell carcinoma. *Nat Commun* 2020;11:4333.
10 Ianiro G, Maida M, Burisch J, *et al*. Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficile* infection: A systematic review and meta-analysis. *United European Gastroenterol J* 2018;6:1232–44.
11 Paramsothy S, Kamm MA, Kaakoush NO, *et al*. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017;389:1218–28.
12 Hänninen A, Toivonen R, Pöysti S, *et al*. *Akkermansia muciniphila* induces gut microbiota remodelling and controls islet autoimmunity in NOD mice. *Gut* 2018;67:1445–53.