A paradigm shift in medicine: autologous fecal microbiota transplantation (FMT), precision nutrition and promotion of proactivity in patients

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A theoretical waste, with enormous beneficial potential

Fecal Microbiome Transplants (FMT), represent a paradigm shift in human medicine. Not in nature, where many animals such as Coleoptera, Lagomorphs, Primates, and Canis practice coprophagy as natural probiotics and nutrient source, and as extra digestion to harvest partially digested compounds [1]. Feces, traditionally considered only as waste, actually are composed by water (75% at a median pH of 6.7), by a diverse community of Bacteria, Fungi, Archaea, helminths, and Virus (25 - 54 % of dry solids), and by undigested carbohydrate, fiber, protein, fat, and inorganic components from the diet, overall with enormous potential in health benefits [2,3].

Fecal Microbiota Transplants, Disruption factors, and Dysbiosis

The concept behind Fecal microbiota transplantation is that many factors are disrupting the healthy balance of our microbiota, such as unhealthy nutrition [4], sedentarism [5], antibiotics [6], pathogens [7], and physical and mental stress [8], and that we can restore it directly introducing a healthy fecal microbiota sample [9-11].

These disruptions produce microbiota dysbiosis [12], meaning a disturbance in the quantitative and qualitative composition of the microbiota, which impairs its functionality regarding phenotypes such as regulation of inflammation and metabolism [13], intestinal permeability [14], immune system [15], B and K group vitamins [16], and neurotransmitters [17]. Similarly, this dysbiosis decreases our allostatic capacity in front of disruption factors, and overall provoking the following negative cycle (Figure 1).

Therefore, theoretical wastes represent an excellent natural tool for the treatment of diseases, as it has been widely proven in the case of recurrent Clostridioides difficile infection [10], inflammatory bowel disease (especially in ulcerative colitis) [18], and recently in systemic sclerosis [11]. FMT has shown overall high efficacy and low adverse side effects [10,11,15]. In the present, it is being explored as a therapy for other more complex conditions associated to gut microbiota dysbiosis such as obesity [19], diabetes [20], autism [21], psoriasis [22], kidney stones [23] or even to more severe symptomatology in COVID-19 infection [24].

Key aspects in the improvement of Fecal Microbiota transplants

Overall, FMT is a powerful tool to interrupt the negative cycle regarding microbiota dysbiosis associated to different diseases, turning to a positive cycle. Although its enormous potential, the widespread dissemination of microbiota transplantation requires to overcome limitations in aspects such as the knowledge of case-effect relationships.

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Table 1. Main research areas and key points in Fecal Microbiota Transplants

| Research area                                      | Key point                                                                 |
|----------------------------------------------------|---------------------------------------------------------------------------|
| Cause-effect relationships                        | design-build-test-learn (DBTL) cycle [25].                                  |
| Super-stool donor recruitment                      | selection and screening [26].                                              |
| Samples management                                  | standardization of collection, preparation and storage of samples [27].  |
| Patient management                                  | Updated monitoring outcomes and ethical issues [27].                      |
| Microbiota banks                                    | guarantying reliable, timely and equitable access to safety transplantation [27]. |
| Disruption factor minimization                      | reinforcing the importance of identifying and minimizing exposure to them [4,8,10,15]. |
| Allostasis against disruption factors               | Improving microbiota by precision nutrition [28], physical activity [29], regulation of circadian rhythms [30], and stress management [17]. |
| Auto-FMT                                           | Avoiding donor availability and recruitment, refuse and side effects; and promoting proactive attitude in patients [31]. |

FMT advances should keep focused on identifying, selecting, and screening super-stool donors for the treatment of specific complex diseases, and on understanding cause-effect roles in each specific dysbiosis [25,26]. Actually, despite the exponential increase of scientific evidence regarding microbiome and FMT potential applications around a design-build-test-learn (DBTL) cycle [25], the biological mechanisms by it works in each case are far from being understood [26].

Similarly, the standardization of methodologies of collection, preparation, and storage of samples is needed, as well as the management of services and patients monitoring outcomes and ethical issues, according to the evolution of applications of microbiota transplantations [27]. All of these advances should be part of the microbiota banks, guarantying reliable, timely, and equitable access to safety transplantation [27].

On the other hand, to reinforce the FMT potential beneficial effect in health, complementary strategies are recommended, such as identifying disruption factors and decreasing the exposure to them to the minimum, recovering microbiota balance, and restoring the intestinal impermeability [4,14]. Conversely, the improvement of the microbiota balance by precision nutrition [28], physical activity [29], regulation of circadian rhythms [30], and stress management [17], will increase the allostasis against the disruption factors. In this context, precision nutrition refers to the one based on the previous knowledge of individual microbiome, genome, physiology, and habits. Its main aim is to determine individual nutritional requirements of prebiotics (bacterial food), probiotics (beneficial bacteria) and postbiotics (metabolites produced by bacteria), by supplements and preferentially by those naturally presented in food [31,32].

**Autologous vs. allogenic Fecal Microbiota Transplantation: a way to promote proactive patients**

In the context of FMT, autologous Fecal Microbiota Transplantation (auto-FMT), represents a promising research area for new health-promoting applications [31,33]. Primarily, auto-FMT can be used to store an optimal state of an individual microbiota and to help to maintain or to restore it against the effect of different disruption factors. Auto-FMT has successfully been used in allogenic hematopoietic stem cell transplantation (allo-HSCT) to restore the patient’s gut microbiota after antibiotic administration of routine treatment [16]. Equally, auto-FMT has been reported as a powerful tool to enhance caloric restriction effects on body weight and adiposity in obese mice [33].

Furthermore, in comparison with allogenic FMT, the auto-FMT shows the advantage of minimizing refuse or unexpected adverse side effects and, in consequence, the necessity of donor selection. Moreover, auto-FMT also means a simplification of screening methodologies. All of those can be especially essential features in a COVID-19 pandemic context [34].

Auto-FMT, as a concept, also implies a paradigm shift in the relationship between patient and medicine. It promotes the change from a relatively passive or expectant attitude to an active, autoresponsible one. From the position of waiting for a donor or a surgery to a proactive approach based on carrying out precision nutrition, and on acquiring healthy life habits, to improve microbiota balance. Reaching its optimal microbiota state could be suitable not only to auto-FMT but also to become in super-stool donor and help other patients in the treatment of different complex diseases.

**Conflict of interest**

The authors declare that there is no conflict of interest.

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