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MICROBIOME TRANSPLANT - FROM AN UNCONVENTIONAL PROCEDURE TO A NEW FRONTIER IN THE TREATMENT OF INTESTINAL DISORDERS

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Abstract

The transplantation of the human microbiota is marked by significant data and personalities that have promoted and maintained an interest in medical practice and scientific research. The long journey in the realm of scientific research and the application of intestinal microbiota in current medical practice has been distinctly separated by the transition from what microbiota is to what the microbiome can do. The remarkable exploration of the therapeutic potential of the microbiome has, however, raised concerns about the associated risks and transformative possibilities that this type of transplant has to offer. From an ethical perspective, the rigorous integration of medical data, medical needs and social health concerns has as a primary focus the potential consequences of microbiome transplantation for personal identity and family relationships. In this paper, we will present how the decision to attempt microbiome transplant treatment provides the opportunity for immediate benefit, but also entails unknown long-term consequences. We will approach this from various points of view such as–informed consent, the determination of what constitutes a healthy donor, the safety and risks of transplantation, the potential exploitation of vulnerable patients, and the implications for public health.

Keywords: microbiome, microbiota, fecal microbiota transplantation, intestinal disorders, transplant, ethics.

Introduction

The transplantation of human microbiota is marked by relevant data and personalities that have promoted and sustained interest in the subject in medical practice and scientific research. Associated with multidisciplinary approaches, ethical intervention has been distinguished by the emphasis on transitioning the microbiome from an unconventional procedure to a new frontier in the treatment of intestinal disorders.

Antony van Leeuwenhoek (1632-1723), the discoverer of the microscope, addressed the Royal Society in London on September 17, 1683, in a letter describing microscopic observations of dental plaque as "very small, very cute animals in motion".

The Russian scientist *Élie Metchnikoff* (1845–1916), with Romanian origins reflected in a complex genetic heritage encompassing five nations, foreshadowed a true revolution through a lecture on the colonization of the child's body after birth. It was believed to be completely sterile until separation from the maternal body. A Nobel laureate (1908), Metchnikoff scientifically promoted the interest in studying microbes and popularized the importance of a healthy microbiome for human well-being.

In 1910, the American physician *I.O. Wilson* performed the first rectal administration of fecal microbiota transplantation. His experiments provided support for a scientific model regarding the use of the intestinal microbiome, with proven effectiveness in treating Clostridium difficile infection.

Doctor *Ben Eiseman (*1907-2012) introduced the transfer of fecal microbiota into the therapeutic regimen for intestinal infections, a procedure considered by Alexander Khoruts more of a form of transplant rather than a medication (Prescott, 2017, Lewandowska-Pietruszka, 2022).

A long journey has been undertaken in medical practice and scientific research on the intestinal microbiome from what it is to what it can achieve.

What is the microbiome?

Human microbiome, a concept developed in 2001 by Joshua Lederberg, Nobel prize in human microbiology in 1958, represents a vast ecosystem of extraordinary complexity that lives symbiotically with the human body (Prescott, 2017). Comprising trillions of microorganisms and their genetic material residing in the intestinal tract, the intestinal microbiome plays a crucial role in the process of digestion and exerts a significant influence on human health. It is considered the *second human genome*, with unique characteristics for each individual, akin to a fingerprint. The use of high-throughput molecular technologies has led to an unprecedented explosion of scientific knowledge and progress in human microbiome research. Analyzing the microbial communities hosted by the human body through DNA/RNA analytical platforms, proteins and metabolites combined with human computing technologies has improved our understanding of the composition, structure and function of the intestinal microbiome. However, this expansion of knowledge has also led to terminological confusion in describing different aspects of these microbial communities and their environments. In terminological usage, the terms proposed by Marchesi and Ravel include (Marchesi & Ravel, 2015):

Microbiota: the set of microorganisms present in a defined environment.

Metataxonomy: the process characterizing the entire microbiota and creating a metataxonomic tree to show the relationships between all obtained sequences.

Metagenome: the collection of genomes and genes from the members of a microbiota.

Microbiome: refers to the whole habitat, including microorganisms, their genome, and the surrounding environmental conditions.

Metabolomics: analytical approaches used to determine the metabolite profile(s) of a given strain or tissue.

Metabonomics: a variant of metabolomics that describes the approach used to generate metabolite profile(s) from complex systems, such as mammals, where more than one strain or tissue contributes to the total accumulation of metabolites, for example, fecal water, urine, or plasma.

What the gut microbiome can do - the ethical perspective

Regarding the ethical perspective, the intestinal microbiome has the potential to influence human health in various ways, including the treatment of intestinal disorders. Ethical interventions and multidisciplinary studies have highlighted the importance of maintaining a healthy microbiome, addressing aspects related to the therapeutic use of fecal microbiota and the use of other techniques. It is crucial to approach these issues responsibly to ensure significant benefits and adherence to ethical standards in microbiome-related medical research and practice.

The ethical debates specific to fecal microbiota transplantation primarily focused on the potential consequences of the procedure for individuals and family relationships, have been comprehensively integrated in the goals of the Human Microbiome Project (2007 the first phase- HMP1, 2014 the second phase, Integrative Human Microbiome Project -iHMP) (Faecal Microbiota Transplantation EU-IN Horizon, 2022). This integration includes medical

data, social health needs, and legal regulations for the procedure. The work of Ma et al. in *"Ethical Issues in Fecal Microbiota Transplantation in Practice"* raises serious ethical and social issues that must be addressed as part of a successful regulatory policy response (Ma et al., 2017; Metselaar & Widdershoven, 2017). Concerns for patient interests in the complex context of fecal microbiota transplantation treatment selection lead to several ethical considerations that healthcare professionals need to carefully tackle. These include informed consent and patient vulnerability, determining what represents a "suitable healthy donor," safety and risk, commercialization, and the potential exploitation of vulnerable patients, as well as the continuously growing number of implications for public health.

Given the impact of the human microbiome on health and human diseases, it is important, for health reasons, to argue these areas of ethical interest with the latest scientific evidence regarding the long-term and unforeseen risks of fecal microbiota transplantation.

Informed consent places emphasis on patient autonomy, especially in sections regarding donor information, risks, health potential, and genetic aspects. Zoya Grigoryan's perspective on the informational component of informed consent aligns with an evidence-based medicine approach. A functional relationship between the medical professional and the patient is crucial, with information about the necessity of the indication, implications, immediate and long-term consequences, as well as the safety of the intestinal transplant procedure (Grigoryan et al., 2020). Leslie Park explores the social perception of the procedure's acceptability, reporting a significant increase in the acceptance rate from 12% to 77% among informed patients. What patients want to know includes information about the risk of disease transmission, the administration of intestinal microbiota, and the discomfort that comes along with the procedure (Park, 2016).

Healthy donor of intestinal microbiota

Healthy donor of intestinal microbiota is an ethically multifaceted area that requires a comprehensive approach.

A first aspect concerns the *gender of the donor,* a theme explored in Suzanne Metselaar's ethical assessment, suggesting the hypothesis that a donor of the opposite sex may induce behavioral and fertility changes in the recipient. Supporting this hypothesis are the results of experimental animal studies indicating higher levels of testosterone in young female mice that received microbiota from male mice (Metselaar & Widdershoven, 2017)). The relationship between microbiota and donor gender associated with increased levels of sex hormones has also been demonstrated in human studies by Song He (He et al., 2021).

Jose C. Clemente, in a review on *"The Impact of the Gut Microbiota on Human Health,"* designates *diet* as a factor involved in the donor-microbiota relationship. *Dietary behaviors* are targeted, particularly those leading to certain diseases such as metabolic and cardiovascular conditions (Clemente et al., 2012).

The medical history of the donor draws attention to the correlation between the microbiome and certain viral infections, digestive cancers, especially colon cancer, and autoimmune diseases.

It is worth mentioning that all these aspects are listed in the donor section of European and Asian guidelines (Cammarota et al., 2017; Shi, 2020). Moreover, the rigorous presentation of these requirements makes recruiting fecal donors for fecal microbiota transplantation a significant and challenging task. Sudarshan Paramsothy, in a study involving 116 potential donors, identified only 12 (10%) donors who met the guideline requirements for fecal transplantation (Paramsothy et al., 2015).

Proximity is another factor correlated with the intestinal microbiota, where the risk of compromising the therapeutic efficacy of the transplanted microbiota is noted in cases involving related donors or those living in the same environment. Alexander Khoruts'

evidence notes the similarity between the microbiome of a recipient patient and their relatives or potential donors from communities with similar dietary habits. The recommendation would be for the donor to be a different person (Khoruts et al., 2009).

Cultural and spiritual issues can become barriers, leading to cultural and spiritual rejection in the context of the donor's dietary habits, which may not be acceptable to the recipient.

Safety and risk

In a generic ethical reformulation, refer to the relationship between risks and benefits. On an evidential level, Shaan Gupta and Lawrence J Brandt Brent specify that in long-term follow-up studies, up to 68 months, no side effects and significant adverse reactions have been reported (Gupta et al., 2016, Brandt et al., 2012). In cases where these events were present, they were successfully managed within the first few hours, at most two days. In practice, fecal microbiota transplantation is considered to be a safe procedure. The theoretical perspective remains focused on the probability of very long-term adverse effects related to infectious diseases or chronic conditions, especially metabolic and cardiovascular illnesses, mediated through the transfer of intestinal microbiota.

Faecal microbiota transplantation as a commercial product

From an ethical perspective, the commercialization of fecal microbiota is related to the categorization of the term within linguistic and vocabulary derivatives with significance suitable for the procedure's counter value. Reporting is done in terms that have connotations for fecal microbiota transplantation, such as probiotics, pharmaceutical products, pills, etc., and which have a selling price (Marchesi & Ravel, 2015). It is concerning that some websites and medical platforms display prices for preparations leading to intestinal transplantation procedures and separately for the procedure itself, estimated at values up to $5400 (Grigoryan et al., 2020). Ethically interpreted, these aspects designate an additional vulnerability area, which, when added to the patient's suffering, whose access to the procedure may be limited due to financial considerations, represents an unfair medical practice approach, with the impossibility of ensuring equal chances for good outcomes.

The impact of faecal microbiota transplantation on public health

This is an aspect that, from an ethical point of view, generates debates that targets both the present and future generations. Considering the proven implications or their probability on public health, the areas of attention, debate topics, and supervisory directions requiring ethical intervention will focus on how descendants may be affected, potential changes in behavior, and treatments for certain diseases.

In this regard, the proven correlation at experimental level and in clinical studies between the microbiome and the impairment of sex cells and fertility raises certain questions about the extent to which descendants may be affected.

Also, considering the connection between the microbiome and possible behavioral modifications, one cannot exclude the individual's desire and even request for behavioral changes through microbiome alteration. This aspect carries profound ethical content related to eugenics, the similarities of which with the effect of biological improvement procedures impose moral validation.

Additionally, if the interactions between the microbiome and a series of conditions, especially those related to metabolic and cardiovascular disease, are considered, the procedure may be a source of potential therapeutic solutions (Metselaar & Widdershoven, 2017).

Although our knowledge of the human microbiome and its impact on health and human diseases is improving remarkably, strong evidence yet to be defined. The scientific consensus that the microbiome is important for humans and significantly affects health and disease does not evade concerns about where the medical and ethical debate currently stands. In this context, the mentioned hypotheses could either become confirmed truths over time or remain unconfirmed statements, currently stored in intestinal microbiota banks. Even regarding stool storage protocols, there are significant variations between institutions, mainly due to the novelty of this treatment approach and the lack of guidelines addressing fecal microbiota transplantation and stool storage.

Conclusion

It is essential to consider the ethical and social aspects of the practical application and ongoing research on the human microbiome to be proactive and prepared for all sorts of challenges. In this regard, the ethical perspective of fecal microbiota transplantation approaches seeks to keep pace with the dynamics and versatility of developments in current practice and scientific research, aiming to cover a broad spectrum and provide solutions to fecal microbiota transplantation related questions. Ethically, there is also a focus on ensuring an appropriate level of protection for the recipient patient, the donor, medical personnel, the nearby and the social community, as well as the fecal microbiota transplantation procedure itself, whose appropriate indication and correct use confirm and enhance its efficiency.

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