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Brief Review

Faecal Transplant Give space after Therapy (FMT): A Promising Therapeutic Tool for Diabetes Mellitus

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Abstract

Alternative approach to treat human diseases with modalities without antibiotics is indispensible due to side effects as well as due to immunity developed by the human body. Naturopathy and Faecal transplant therapy are focussed in therapeutics worldwide. Human trials as well as animal model studies are done to understand the efficacy of these modalities for different diseases including diabetes mellitus (T2D). Faecal transplant therapy has been declared as standard to treat recurrent *Clostridium difficile* infection after undergoing experimental studies to understand the pros and cons of the technique. Here we summarise the recent results of similar studies pertaining to diabetes mellitus.

Introduction

The mighty microbiota are powerful creatures that come to this universe 3 billion years ago and dominated the biosphere continually [1,2]. Man came later approximately 2 million years ago [3]. All humans get the seeds of microbes from mother during the birth except those who take birth by caesarean section [4,5]. These seeds multiply along with the growth of the human body may be faster than human body cells and it is estimated the number to a range of 39 trillion even more than the number of human body with 37 trillion cells [6]. This miniature mighty microbiota recently gets focussed due to their ability to regulate diverse functions in human body [7]. Composition of the microbiota differs in different regions of the digestive tract according to age, body weight and diet. These gut microbiota are responsible for regulating many functions such as gut wall integrity, innate immunity, fertility in human metabolism etc [8-12]. The functional significance of the microbial genes influencing key metabolic processes, such as breakdown of indigestible dietary fibres to short-chain fatty acids, biosynthesis of amino acids and vitamins, energy metabolism, metabolic signalling, formation of the immune system, regulation of integrity and mobility of the gut barrier, production of neurotransmitters and hormones cannot be overlooked [6].

Scientist have identified a two-way cross talk through gut-brain axis between microbiota, immune and neuroendocrine system, as well as of the autonomic and central nervous system [13]. Zhao *et al.,* suggested the existence of gut - kidney axis indicating the relationship between the gut microbiome and renal diseases including diabetic nephropathy [14].

It is interesting to understand the influence of circadian rhythm on intestinal microbiota and vice versa inducing a broad spectrum of diseases such as metabolic endotoxaemia, inflammation, impaired glucose metabolism, insulin resistance, obesity [15,16]. The dysbiosis of the gut microbiota contribute to the development of metabolic syndrome, T2D, inflammatory bowel diseases, autoimmunity and carcinogens and dysbacteriosis [17,18,19].

T2D is due to insufficient insulin production from beta cells, and is a highly prevalent metabolic disorder characterized by an imbalance in blood glucose level, altered lipid profile and high blood pressure. Genetic constituents, high-fat and high-energy diet and a sedentary lifestyle are three major causal factors for the high risk for the prognosis of T2D [19].

According to the latest International Diabetes Federation (IDF), the global prevalence of T2D in adults was 536.6 million people (10.5%) in 2021, and that there would be 783.2 million people (12.2%) living with diabetes worldwide by 2045 [20]. In addition to metabolic abnormalities, both obesity and diabetes are associated with increased risk of neuropsychiatric and mood disorders, including poorer cognitive performance,

increased rates of depression, anxiety and dementia altogether a social burden.

Involvement of Gut Microbiota in Metabolic Syndrome

In the present scenario, prevalence of metabolic syndrome and its manifestation proves to be a cluster of symptoms such as insulin resistance, dyslipidemia, high blood pressure and increased abdominal girth, which are strongly associated with the development of T2D and cardiovascular disease proves to be global health problem.

A solid base of evidence has linked "leaky gut" permeable to bacteria and/or bacterial components into the system in several diseases. A different approach to demonstrate impaired intestinal barrier function is by looking for bacterial signatures in the circulation. Gut microbes are also reported to affect gut permeability, and thereby are important in type 1 diabetes pathogenesis. It has also been proposed that increased gut permeability might result in pancreatic β-cell damage due to the increased absorption of exogenous antigens. Some microbial toxins have been reported to directly impair pancreatic β-cell function [22].

Functional significance of the beneficial strains of gut bacteria in T2D is identified. For example *Akkermansia muciniphila*, decreased gut permeability using extracellular vesicles which improve intestinal tight junctions in the epithelium. Studies show that the supernatant from the cultured *Faecalibacterium prausnitzii*, bacterium enhances the expression of tight junction proteins improving intestinal barrier functions in colitis model. Butyrate, produced by *Faecalibacterium, Roseburia,* also has a potential role to reduce gut permeability through serotonin transporters and peroxisome proliferator-activated receptor-γ (PPARγ)-dependent pathways . *Akkermansia muciniphila* and Lactobacillus *plantarum* reduce the expression of hepatic flavin monooxygenase 3 (Fmo3), a key enzyme has been found to prevent development of hyperglycemia and hyperlipidemia in insulin resistant mice. Microbiota and their products can modulate gut hormones and enzymes to improve insulin resistance and glucose tolerance. *Akkermansia muciniphila, Bacteroides acidifaciens, Lactobacillus gasseri* have been reported to increase fatty acid oxidation in the adipose tissue. Likewise, butyrate produced by gut microbiota is found to promote fatty acid oxidation and thermogenesis by inhibiting the histone deacetylation process in the muscle which increases energy expenditure partially by promoting mitochondrial functions in the muscle. In liver and adipose tissue, butyrate and other two short chain fatty acids (SCFAs), propionate and acetate, decrease the expression of PPAR-γ which in turns increases fatty acid oxidation. Hence, members of microbiota with beneficial effect on T2D modulate metabolism of glucose and fatty acids and associated energy expenditure in the host that results in alleviation of obesity accompanying T2D [23].

Sato et al., were the first one to report information on gut microbiota in the systemic circulation of Japanese patients with type 2 diabetes. Gut bacteria were detected in blood at a significantly higher rate in diabetic patients than in control subjects (28% vs. 4%, $P < 0.01$), and most of these bacteria were Gram-positive [24]. Endotoxemia, i.e. the presence of lipopolysaccharide (LPS) in the blood, is a clue for translocation of gram-negative bacteria. LPS infusion in rodents showed an increase in insulin resistance to a similar extent as a high-fat diet. Evidence in humans are still wanting [25]. Halmos and Suba (18) suggested that short-chain fatty acids emerging from fermentation of carbohydrates develop into the intestines, which produce butyrate, acetates and propionates with favourable effects on different metabolic processes .From the membrane of Gram-negative bacteria LPS penetrate into the blood stream via impaired permeability of the intestinal mucosa. These processes induce metabolic endotoxaemia, inflammation, impaired glucose metabolism, insulin resistance, obesity, and contribute to the development of metabolic syndrome, type 2 diabetes, inflammatory bowel diseases, autoimmunity and carcinogenesis [18].

To understand the role of the gut microbiome and brain insulin resistance Soto et al., evaluated behaviours and insulin action in brain of mice with diet-induced obesity (DIO) with and without antibiotic treatment [26]. They observed that DIO mice expressed increased anxiety and depression indicating decreased insulin signalling and increased inflammation in the nucleus acumens and amygdale. These changes are transferrable to germ-free mice, and are associated with modifications in the levels of neurotransmitters and other metabolites, which can affect brain functions. The authors concluded that changes in gut microbiota can control brain insulin signalling and metabolite levels leading to altered nervous behaviours [26].

Zhao et al. studied the composition and function of the gut microbiome of 137 patients with diabetes and 179 age- and gender-matched healthy controls. They found decrease in α-diversity of bacterial taxa in the T2D group as well as a decrease of *Bacteroidetes* and a marked increase of *Proteobacteria, Actinobacteria*, and *Verrucomicrobia.* At the genus level, *Bacteroides* and *Prevotella* decreased the most, while *Escherichia-Shigella, Lachnospiraceae incertae sedis, Subdoligranulum, Enterococcus*, and *Klebsiella* had different degrees of expansion in the T2D group. The faecal microbial community had an obvious alteration in patients with T2D in both composition and function so it is even possible to distinguish diabetics from healthy individuals [14]. In 50Japanese patients Sato et al., observed counts of the *Clostridium coccoides* group, *Atopobium* cluster, and *Prevotella* (obligate anaerobes) were significantly lower ($P < 0.05$), while the counts of total Lactobacillus (facultative anaerobes) were significantly higher ($P < 0.05$) in faecal samples of diabetic patients than in those of control subjects. Especially, the counts of Lactobacillus *reuteri* and *Lactobacillus plantarum* subgroups were significantly higher ($P < 0.05$) [24]. Falony *et al.,* reported that one specific bacteria that has been the focus of several obesity and T2D studies is the mucus-colonising *Akkermansia muciniphila* [27]. Zhang et al., found *A. muciniphila* to be decreased in individuals with prediabetes (impaired glucose tolerance and/or impaired fasting glucose) and newly diagnosed T2D, and suggested that low abundance of this bacteria could be a biomarker for glucose intolerance [28]. More recently, *A. muciniphila* was observed to be decreased prior to the onset of T2D in twins, while high abundance was associated with a healthier metabolic status in overweight/obese humans. In addition, greater improvements in glucose homoeostasis and body composition results after energy restriction [6].

Studies give strong evidence for the insufficient consumption of indigestible carbohydrates and loss of bacterial species in the human gut that rely on these substrates resulting in the decreased production of their fermentation end-products, short-chain fatty acids (SCFA). Epidemiological studies also substantiate the inverse association between dietary fibre and the incidence of T2D. Dietary fibre and whole grains have been shown to increase the diversity of the human gut microbiota bacterial genus *Prevotella* to maintain health. Analysis of the gut microbiota will pave way to gain an understanding of

individual responses to dietary interventions [6].

Falony *et al.,* investigated the association between 503 clinical-, health- and lifestyle-related variables and they suggested that the diversity and composition of gut microbiota among 1106 Belgian individuals and also in a replication cohort (Dutch Life Lines DEEP; n = 1135). The disparity in the occurrence of different species of bacteria in the gut probably due to the differential range of health and environment factors associate with changes in the composition and functionality of the gut microbiota [27].

Reports on the dysbiosis of the gut biome as a contributory factor in rapid progression of insulin resistance in T2D that accounts for about 90% of all diabetes cases worldwide is available. This dysbiosis may be responsible for reshaping the intestinal barrier functions and host metabolic and signalling pathways resulting in insulin resistance in T2D. The metabolites from the microbes interact with the epithelial, hepatic and cardiac cell receptors that modulate host physiology. Any change in the gut microbiota can shift the host metabolism towards increased energy harvest during diabetes and obesity [20].

Mechanism of Regulation by Microbiota in T2D:

Bacteria strains resistant to antibiotics will skew gut microbiota composition resulting in the lack of diversity in the gut microbiome and is implicated in an underdeveloped immune system. The western diet containing only half of the recommended intake of 30 g of fibre daily accompanied with low intake of dietary fibre results in generating SCFAs as metabolites by the gut microbiota. SCFAs exert systemic anti□inflammatory effects by producing immunoglobulin A and immunosuppressive cytokines. Number of bacteria involved in SCFA production was significantly lower in people with type 2 diabetes and it has been observed that SCFAs play vital roles in type 2 diabetes [22]. Loss of early□life exposure to bacteria [8], due to the increased use of antibiotics and a decrease in fibre intake results in dysbiosis a causal factor for increased incidences observed in inflammatory diseases, including T2D worldwide. SCFAs join with G□protein coupled receptors, resulting in the following biological effects of SCFAs is to promote secretion of glucagon□like peptide□1, an important insert in hormone, which is made by enteroendocrine L cells. This peptide hinder the secretion of glucagon, interfering with gluconeogenesis in the liver, improves insulin sensitivity, result in bodyweight loss and directly hinder the low□grade inflammatory response caused by bacterial migration from the intestines into the mesenteric adipose tissue and the blood.

The interactions among gut microbiota□derived metabolites and the host immune system is through various signalling pathways involving chemical communications. This chemical communications control metabolic reactions through choline, phenols, bile acids, and SCFAs produced by both the gut microbiome and host genome that is indispensible for and vital to health.

The gut biome studies provides a hint that the Gram negative *Bacteroidetes* and *Proteobacteria* might induce the pathogenesis of T2D through an endotoxin induced inflammatory response as the endotoxin, LPS exists in high concentrations as a main outer cell membrane component. This must be the reason for the low levels of butyrate□producing gut microbes in T2D patients resulting in the progression of disease pathogenesis [22]. T2D is attributed with elevated levels of pro-inflammatory cytokines, chemokines and inflammatory proteins. Some strains of gut microbes and microbial products especially LPS promote metabolic endotoxemia and low-grade inflammation, while others stimulates anti-inflammatory cytokines and chemokines. For example, induction of IL-10 by species of *Roseburia intestinalis, Bacteroides fragilis, Akkermansia muciniphila, Lactobacillus plantarum, L. casei* may contribute to improvement of glucose metabolism since overexpression of this cytokine in the muscle protects from ageing-related insulin resistance . *R. intestinalis* can also increase.
Interleukin-22(IL-22)production, an anti-inflammatory cytokine known to restore insulin sensitivity and alleviate diabetes. It can also promote T regulatory cell differentiation, induce Transforming growth factor-β (TGF-β) T and suppress intestinal inflammation. Likewise, *Bacteroides thetaiotaomicron* induces expression of T regulatory cell gene expression.

Inhibition of pro-inflammatory cytokines and chemokines is another route used by beneficial microbes to prevent inflammation. Various species of Lactobacillus *(plantarum, paracasei, casei)* can decrease Interleukin 1β (IL-1β), Monocyte Chemo attractant Protein-1, Intercellular adhesion molecule-1, Interleukin -8 (IL-8), CD36 and C-reactive *protein. L. paracasei* and *B. fragilis* inhibit expression of Interleukin -6 (IL-6). Similarly, *Lactobacillus, Bacteroides* and *Akkermansia* have been found to suppress Transforming growth factor -α (TNF-α). *L. paracasei* and microbial anti-inflammatory molecule from *F. prausnitzii* inhibit the activity of Nuclear factor-κB (NF-κB) . Similarly, *Roseburia* and *Faecalibacterium* are butyrate producing bacteria and butyrate is also known to inhibit the activity of NF- κB. *Lactobacillus casei* and *Roseburia intestinalis* decrease another pro-inflammatory cytokine.

Interferon gamma (IFN-γ) whereas *Roseburia intestinalis* can inhibit Interleukin-17(IL-17) production. *Bacteroides thetaiotaomicron* reduces Th1, Th2 and Th17 cytokines in mono-associated mice .Potentially detrimental microbes in T2D (pathobionts), like *Fusobacterium nucleatum* and *Ruminococcus gnavus* can increase several inflammatory cytokines, albeit in other inflammatory diseases [23]. Vrieze *et al.,* in their study subjects received faecal transplants from lean individuals (allogenic transplantation) their insulin sensitivity improved as well as the abundances of butyrate- producing bacteria were also increased. This observation was in concordance with increased microbial diversity compared to subjects who received autologous transplantation (stool from self) after a 6 week period. Taking these results into account, type 2 diabetes patients only presented with elevation in abundances of several opportunistic pathogens and a reduction in numbers of beneficial butyrate- producing bacteria [29].

At present, little is known about the relationships between type 1 diabetes (T1D) and the gut microbiota. Bosi *et al.,* from their clinical study involving 81 T1D patients with intestinal abnormalities and 40 healthy subjects, showed that intestinal permeability was significantly increased in the T1D patients as compared with healthy individuals, indicating that poor intestinal barrier function could contribute to T1D pathogenesis. The ongoing larger cohort studies, such as The Environmental Determinants of Diabetes in the Young currently in progress, may come out with results to define alterations in the human gut microbiota composition and the mechanisms responsible for the prognosis of autoimmunity and onset of T1D [30].

Faecal Microbiota Transplantation FMT

Taking antibiotics too often or for the wrong reasons can alter the infectious in the tissue microenvironment and may reduce the

ability of immune cells to kill bacteria therefore scientists were looking for alternative approach to antibiotics such as FMT [31]. In the present scenario studies on the role gut microbiota in the treatment of T2D endorses that bariatric surgery remodels the gut microbiota composition; therapeutic effects of metformin are mediated by gut microbiota; personalised nutrition, diet and prebiotics modify the quality and quantity of gut microbiota. Instead of roundabout way the best option is to clear the gut and allow only microbiota to maintain disease free healthy gut. But it is worth noting that not all participants respond to the FMT in the same way.

FMT is a procedure that delivers healthy human donor stool to a patient via colonoscopy, enema, nasogastric (NG) tube, or in capsule [32]. FMT has emerged as highly effective, safe, and cost-effective treatment option at least for recurrent *Clostridioides difficile* infection (CDI) with a success rate around of 90%. The U.S. Food and Drug Administration recently approved the latest faecal microbiota transplantation, or FMT, therapy product for recurrent CDI. Formal approval was granted for Rebyota® for patients 18 years and older who have completed antibiotic treatment for recurrent CDI but had ineffective results [33]. In addition to CDI infection this technique give positive results from few trials using animal model as well as human trials in treating brain diseases such as Alzheimer's, Huntinton, Parkinson's, autism, and non nervous bacterial diseases caused by *Carbapenem-resistant Enterobacteriaceae (CRE),* arthritis, diabetes mellitus, inflammatory bowel disease, and obesity, polycystic ovary endometriosis, etc [34-39].

In a pilot study the first human trial of 18 individuals, FMT from lean individuals to men with the metabolic syndrome resulted in significant improvements in peripheral insulin sensitivity along with an increase in butyrate-producing bacteria in the recipient's faecal microbiota, which is in line with observational studies where butyrate-producing bacteria have been observed to be enriched in the faeces of healthy individuals. However, this study was small, it did not report data on glucose levels during the intervention and it has not yet been replicated. Moreover, not all participants responded to FMT, again raising the question as to why some individuals are responsive while others are not [6].

The FMT has the propensity to improve the functioning of the host bacteria and completely remodel the entire host microbiome by altering the actual composition and ratio of the resident species present in the host. In terms of risk, FMT is considered a very safe procedure; however, some adverse effects have been documented. Any reported deaths succeeding FMT are few-and-far-between and is often a result of comorbidities with unrelated disease processes, and are not related to the actual FMT procedure itself [40].Theoretically, the transfer of infectious pathogens from donor to recipient can and does occur, but the intense pretreatment screening process greatly minimizes this risk. The at risk population for fatal adverse reactions are the immune-compromised, such as HIV patients and patients under immunosuppressive drug therapy [40,41].

Conclusion

Many of the observed physiological changes after FMT treatment are anti-diabetic in nature including improved glucose handling, basal metabolic rate enhancement and lower levels of systemic inflammation. Although there are still many unknowns surrounding to FMT, new discoveries will continue to bridge these gaps in our understanding of FMT to standardize the protocol to improve metabolic disorders related to gut dysbiosis like obesity and diabetes.

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