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REVIEW ARTICLE

FECAL MICROBIOTA THERAPY AND ITS POTENTIAL IN MEDICAL PRACTICE

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Summary

Fecal microbiota therapy is going through its renaissance period. Even in ancient China, stool and its derivats were used for therapy of various diseases. Now thanks to new molecular methods a new knowledge about the intestinal microbiome and its interference with the human physiology, this method can be used for concrete therapy of disease.

Key words: fecal microbiota therapy; Clostridium difficile; infection; immunocompromised patients

INTRODUCTION

The human body is home to trillions of bacteria, which is 10 times more than the number of cells in the body. Most of the bacteria of our body are localized in the intestine. There are up to 36 thousand bacteria capable of inhibiting the gastrointestinal tract, most of which are yet to be differentiated. Each person has 500 to 1000 species of bacteria in their gastrointestinal tract. The microbiota consisting of bacteria, eukaryotes, viruses, and archaeon of the gut are in a close symbiosis with the human body and can influence the entire organism both directly and indirectly [1, 2, 3]. Most types of bacteria that colonize our body cannot yet be cultivated by existing microbiological methods, but a gateway to deciphering the human microbiome has opened with new molecular biological methods such as 16S RNA gene sequencing [1, 2].

With the evolution of these new technologies, new projects are organized such as The Human Microbiome Project, which is built by the National Institutes of Health to research the links between human microbiome and disease in humans [2, 4].

The main part of development of a human microbiota happens in the first year of a person's life. The bacteria produce a number of molecules that closely interact with the human intestine, immune system and other parts of the host organism.

Four main phyla dominate the population in the human intestinal microbiome –*Bacteroidetes*, *Firmicutes, Actinobacteria* and *Proteobacteria* [2, 4].

The epithelial cells of the intestine are covered by a layer of glycocalyx and mucous gel. Its main

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function is to nourish bacteria which are commensal to the human intestine and serve as a barrier to those that are pathogenic, this has a clear effect on the composition of the microbiota. The gel layer is actively regulated and differs in thickness and composition in different part of the intestine and is constantly renewed [5, 6]. Due to the absence of effective and safe treatment for certain diseases, interest in microbiome based therapies is at rise. Diseases that are derived from disturbances of the homeostasis of the human microbiome or dysbiosis such as *Clostridium difficile* infection or idiopathic bowel disease can be potentially treated and even cured by fecal microbiota therapy [7, 8].

Fecal microbiota therapy has many synonyms such as human probiotic infusion, stool transplant, fecal transplant. This procedure has been a question of great interest in the recent years mainly due to the increased burden of *Clostridium difficile* infection [9, 10].

Fecal microbiota therapy has been known to modern medicine since 1958; even so, the precise mechanism of action of this procedure in restoring gut function is not yet fully understood. It is speculated that the fecal microbiota transplant restores the structure and composition of the colonic community and therefore suppresses the growth a toxin formation of *Clostridium difficile* and possibly other pathogenic bacteria [4, 11].

Short history

The first mention of fecal microbiota therapy dates back to the fourth century ancient China where Ge Hong treated different maladies with fecal matter such as food poisoning and other gastrointestinal disease, but also other symptoms, like fever. Later findings bring us back to China with Li Shizhen who gave this therapeutic method a more sophisticated name of "yellow soup" which was also fecal matter dissolved in a liquid and used for treating consti-pation, diarrhea and other diseases of the gastrointestinal tract not only in humans, but also in animals [12]. The next big name which had an impact in fecal microbiota therapy was Christian Franz Paullini, a German physician who worked in the seventeenth century. He also treated patients with gastrointestinal disturbances, other bodily materials such as urine was used in treatment of other diseases. He left traceable works on the matters of his investigation, which have been preserved until this day.

The first modern day application of fecal matter was in 1958 when Dr. Ben Eisman and his team who treated patients with fulminant pseudomembranous colitis with an enema of fecal matter with a positive effect and full recovery of the severely ill. It is speculated that the pseudomembranous colitis may not have been caused by *Clostridium difficile* [8].

Safety

There are yet to be case reports on adverse effects which can be traced back directly to fecal microbiota therapy, there are no cases of acquired infections, even with immunocompromised patients, even though the donor screening schemes differ from country to country. The only potentially harm can be caused via endoscopic methods with direct trauma from the endoscopic tools. There are a few speculated cases of obesity which evolved after fecal microbiota therapy, however a direct cause is still to be proven.

Ethical aspects

A few questionnaire based studies were conducted to find out the attitude of patients towards potential fecal microbiota transplant. The patients for whom fecal microbiota transplant is a potential therapy are more reserved than the caregivers of patients for whom fecal microbiota transplant is considered. Test subjects consider fecal microbiota transplant as the more "natural" treatment and, therefore, the safer option compared to standard medications. Potential patients consider probiotics to have the same effect as fecal microbiota transplant.

The major ethical aspect is the method of administration of homogenized stool. Routes through which this can be done are nasogastric tube, colonoscopy and enema. Nasogastric route of administration was least appealing to patients. Potential recipients prefer their relatives to be donors.

Another aspect of concern is whether donors are thoroughly screened for potential transmittable disease and the risk of gaining diseases that are not routinely screened for or diseases that are not infectious in origin. The initial disgust does not alter patient's interest in fecal microbiota therapy and would not play and important role if this therapy was considered helpful [13]. Neither religious, nor cultural aspects play a role in making a decision [15, 16]. A colorless, odorless pill would be the preferred method of application if possible. The amount of people interested in fecal microbiota therapy is the same

percentage in both sexes. However the reasons why people would not consider fecal microbiota therapy do differ, men are more concerned by the safety aspect of the procedure, whereas women are more discouraged by the possible disgust by the procedure. Neither age, nor level of education had any impact on the potential decision. People considered the aspect of discussing the procedure with the potential donor as the most unappealing of all the factors.

Procedure of transplantation

Fecal mirobiota therapy involves collecting stool from a healthy donor who has been screened for transmittable diseases such as HIV, hepatitis A, B and C, syphilis, intestinal infections and other disease. The potential donor should be of general good health with no known chronic diseases including, for example, atopic disease, obesity, hypertension, and so on. The stool is then prepared and administered to the patient [12, 14, 15].

Routes of administration

There are three main routes of admission of fecal microbiota therapy - naso-duodenal, transcolonoscopic or enema based.

The naso-duodenal route may be complicated by vomiting and aspiration, colonoscopic route risks damage of the colonic mucosa, but the microbiota is delivered directly to the predicted place of action. Enema administration is the safest and cheapest method of administration and can also be administered without the assistance of a doctor or any other healthcare professional for that matter by the patient himself outside a healthcare facility. So far, it seems that the methods of administration through the lower parts of the gastrointestinal track have a higher cure rate for infection with *Clostridium difficile* compared to the naso-gastric route, although in different studies comparing the routes of administration differed in the amount of homogenized stool used for either route. The route of administration depends on the type of patient. In more severe forms of colitis, a gentle enema can be the best choice, but it does not offer a view of the colonic epithelium like colonoscopy in patients with underlying gastrointestinal disease, for example, and stool can be delivered via eye control in places that can be hard to access such as diverticules, in severe forms of colitis there is a risk of perforation and an experienced endoscopist is crucial. Fecal microbiota therapy does not seem to work in patients with *Clostridium difficile* infection post colectomy [10, 17–19].

Another more modern and esthetic form of fecal microbiota therapy is capsules filled with homogenized fecal bacterial matter, another potential method of administration. Stool not more than 6 hours after defecation is applied into sterile vessels sealed by plastic, after that the top coat is disinfected again. These formed capsules are frozen at -80 °C and kept at -20 °C. Prior to use these capsules are thawed. In some studies centrifuged supernatant of fecal matter is used, which allows a smaller amount of stool ending up to 8-12 capsules. The cumulative cure rate of these patients is comparable with other routes of administration [20, 21]. Certain companies, mainly in the USA, offer stool from prescreened donors. This stool can be ordered directly and delivered to a patient's home to be administered via enema. The screening of one donor with his fecal matter being transplanted to a larger number of patients significantly reduces the cost of therapy when a donor doesn't have to be screened per patient. These donors are paid for their fecal matter [22].

Clostridium difficile infection

Clostridium difficile is a gram-positive, rod-shaped, spore-forming bacterium which spreads from one person to another through fecal-oral route. Spores can survive the stomach acidity and can germinate in the gut. This organism can outgrow the normal flora leading to the disease. *Clostridium difficile* can flourish in an anaerobic environment, but can survive on different surfaces for long periods of time. The eradication of these spores isn't easy and cannot be done by regularly used disinfectants.

Clostridium difficile produces toxins which can cause inflammation and disrupt the mucosa causing diarrhea. When toxins get into the intestinal cell, they interfere with cell function causing cell death.

Toxin A is an enterotoxin which causes increased intestinal permeability and the secretion of fluids, Toxin B is a cytotoxin which leads to colonic inflammation. All of these toxins cause the loss of barrier function of the intestine making granulocytes infiltrate the intestine and support diarrhea.

Clostridium difficile infection is the most common health care-associated infection of the last decade, it is a public health matter of first priority and also an enormous economic burden, a disease

with a high morbidity and mortality rate, which greatly alters the quality of life of diseased patients. The complications are severe and life threatening. The incidence of severe and recurrent *Clostridium difficile* infections is on the rise.

Clostridium difficile infection is the perfect condition for fecal microbiota therapy. The primary cause of the disease is intestinal microbiotic dysbiosis, and *Clostridium difficile* overgrowth. When treated with antibiotics, *Clostridium difficile* is killed, but the intestinal microbiota is damaged even more, leading to relapse rates of 20% where this number rises with every subsequent *Clostridium difficile* infection episode and every following antibiotic treatment. Altogether antibiotics in mono and combined therapies fail to eradicate this disease, because they do not restore the correct flora, Vancomycin and Metronidazole alters microbiota diversity further, Vankomycine targers grampositive aerobic and anaerobic bacteria, whereas Metronidazole targets mainly anaerobes. Fidaxomicin is another drug of choice, this drug doesn't alter the microbiota as much as other antibiotics, has a higher cure rate and a lower relapse rate compared to other antibiotics used for treatment of Clostridium difficile infection, however, so far a very important aspect against therapy with Fidaxomicin is it's very high cost. All of this leads to a need of a creative approach in new treatment methods. Fecal microbiota therapy amongst other positive aspects is relatively inexpensive and not only does it eradicate *Clostridium difficile*, it also restores deficient intestinal bacteria. This makes fecal microbiota transplant the most effective therapy for relapsing *Clostridium difficile* infection. The cure rate is around 90%. In the last few years, fecal microbiota therapy for treatment of *Clostridium difficile* infection has transferred from being the" last resort" treatment to a mainstream therapy method and is a known part of most *Clostridium difficile* infection guidelines, including the ones for Europe including the Czech Republic in particular [23].

The microbiota of patients susceptible to *Clostridium difficile* infection is altered, there is a reduced amount of *Bacteroidetes* and *Fermicutes* most probably caused by previous antibiotic treatment, this deficiency most likely facilitates the growth of *Clostridium difficile*; however, the precise mechanism of action of fecal microbiota therapy remains unknown.

New hypervirulent ribotypes 027 and 176 are on the rise. Infections with these ribotypes are in general more vicious and severe and are followed by a higher colectomy rates and higher mortality in comparison with previous decades. The strains are unique in a higher toxin-producing potential, they also express binary toxin, and this leads to poorer treatment outcomes.

Different centers that offer fecal microbiota therapy have different protocols of quantity, method of infusion, methods of preparation of recipients and donor differ, there is no standard protocol in our country either [7, 9, 23–25].

Adverse effects

No significant adverse effects have yet been described, discomfort such as mild diarrhea and dyspepsia may occur which is usually resolved spontaneously shortly after treatment [10, 26, 27]

The immunocompromised recipients

There are limited studies of immunocompromised patients receiving fecal microbiota therapy; there are no described cases of infection resulting from this procedure.

Clostridium difficile infection is the most common intestinal infection in the adult immunocompromised hosts such as patients with AIDS andsolid organ transplant recipients whereas not all of these patients have known prior antibiotic exposure, therefore immunocompromision is an independent risk factor for infection with *Clostridium difficile*, and both innate and adaptive immune mechanisms play a role in protection against *Clostriudm difficile*. Signaling includes recruitment of neutrophils in the location of inflammation. Immunocompromised patients have multiple out-patient visits and extended periods of hospitalization and are often treated by broad-spectrum antibiotics. All of this plays a major impact in *Clostridium difficile* infection. *Clostridium difficile* infection together with idiopathic bowel disease is also a major problem. The mucosal barrier of the intestine in the patient with idiopathic bowel disease is disrupted, immunocompromising therapy is also a risk factor and all of this increases the risk of *Clostridium difficile* infections in these patients three fold compared to healthy population. Most patients treated for *Clostridium difficile* infection with fecal microbiota therapy had a positive effect after the first dose of therapy, the effect is similar to that of patients with *Clostridium difficile* infection without immunocompromision.

There are no deaths related to infection in this group of patients. However, deaths related to the procedure of application of fecal material were described in literature. Some people with severe immunocompromise with idiopatic bowel disease did need colectomy followed by fecal microbiota therapy due to disease flare. These studies are based of retrospective studies and more information is needed [9, 23, 28–30].

The role of microbiota in altering the brain

200 to 600 million neurons connect the human gut and brain, the bidirectional gut-brain axis is a point of investigation in many studies. Changes in the gut microbiota of rodents occur after they are exposed to stress and begin showing signs of anxiety-like behavior and depression, also maternal separation of rat pups leads to increased intestinal permeability and altered microbiota, these changes remain until the rodent's adulthood. In rhesus monkeys this separation leads to decrease in lactobacilli in feces and increased susceptibility to infection.

Campylobacter jejuni infection is correlated with increased anxiety. Interventions with *Bifidobacteria* strains decrease depressive and anxiety behavior.

This effect of probiotic strains seems to be mediated by the Vagus nerve, the metabolites of microbial colonization initiate signaling mecha-nism of neuronal circuit which lead to behavior such as anxiety and decreased motor control. Also neurodevelopmental disorders such as autism spectrum disorders are linked not only to environmental factors such as exposure to pollution, chemicals, drugs, maternal stress, maternal infection, but also to microbiota composition, with the alteration of which the coursed of disease can also be slightly altered [31-33].

Autism spectrum disorders

Autism spectrum disorders are neurodevelopmental dysfunctions characterized by impairment of capability of communication and social interactions. Among other symptoms, patients with autism spectrum disorder are prone to have gastrointestinal problems such as diarrhea, bloating and other dyspeptic problems. The intestinal permeability of these patients is increased. This seems to be caused by altered composition and metabolic activities of intestinal flora. Environmental and genetic factors seem to play an important role in the development of those symptoms. A few studies have observed an effect of Vancomycin treatment and certain diet changes, which alters not only the microbiota of patients, but also social functions of patients with autism spectrum disorders. In comparison with healthy control groups, the microbiota of patients with autism spectrum disorders have more *Clostridia*, *Bacteroidetes*, *Desulfovibrio* and *Sutterella* spp and lower levels of *Firmicutes* and *Verrucomicrobia*, also the composition of *Lactobacillus* a *Bifidobacterium* species differ in patients with autism spectrum disorders compared to healthy control groups, including healthy siblings and family members who share household. However, these observations are not consistent. Some studies do not observe any significant changes in the microbiota in patients with autism spectrum disorders compared to healthy individuals. There are certain limitations to a high-quality microbiota observation in these patients, because control groups and patients differ in age, presence of concomitants and gastrointestinal diseases, the control groups are usually members of a common household. There is hope that a more thorough observation will be conducted with the use of new bacteria detection methods. Another aspect which helps the theory that microbiota is altered in patients with autism spectrum disorders is the fact that patient treated with Vancomycin improve both in gastrointestinal and cognitive symptomology. However, antibiotic use does not have a long term effect.

It seems that bacterial toxin over-abundance might be involved in pathogenesis of autism spectrum disorders, for example some *Clostridiaceae* synthesize metabolites like phenols and indole derivates which are toxic for humans. The potential of spore-forming is a concern of relapsing autism symptoms after Vancomycin treatment. 31. Metabolites produced from the fermentation of undigested food differ depending on the composition of the microbial flora, more specifically the levels of butyric, valeric, propionic and acetic acids, amino acids and free amonia. All of these metabolites are increased in children with autism spectrum disorders.

Few studies of administering fecal microbiota ther-apy have shown to have positive, although not lasting, outcomes [31–34].

Inflammatory bowel disease and microbiota

Inflammatory bowel disease is a term for a group of idiopathic, chronic, and relapsing inflammatory disorders of the gastrointestinal tract. Specific changes in microbiota were described: *Bifidobacteriam*, *Lactobacillus* and *Faecalibacterium prausnityii* seem

to be decreased, and mucosal-adherent bacteria are increased. The metabolites of *Firmicutes* are mostly short-chain fatty acids such as butyric acid, which is a substrate with strong immunoregulatory properties. This is shown by a described positive effect in patients with ulcerative colitis who were treated by enemas with butyrate. Main treatment for ulcera-tive colitis includes steroids, aminosalycilates, immunosupressants including corticosteroids and biologic therapy. Not only are all these standard therapy regimens usually complicated by adverse effects, but there are still a number of patients who remain refractory to these therapies and require surgery. Those patients who do have an effect on therapy usually have to cope with mild lasting symptoms and a lower life quality.

Intestinal microbiota has been suspected as an ethiopathologic aspect of idiopathic bowel disease and different treatment regimens with probiotics a prebiotics where tested with variable evidence of efficacy. An alternative management in altering the gut microbiota is management with fecal microbiota therapy where *Clostridium difficile* infection is more common in patients with idiopathic bowel disease [25, 35–37].

Ulcerative colitis

Ulcerative colitis is an idiopathic inflammatory bowel disease confined most commonly to the rectum and colon from the gastrointestinal tract. It is suspected that the immune response to fecal flora is inappropriate, thus causing an inflammatory response as part of the ethiopathogenesis, however no specific organism has yet been identified as the culprit. There are documented cases of long term remission without the need of immunosuppressive therapy after fecal microbiota therapy, this greatly increases the quality of life in these chronically ill patients [16]. The patients with ulcerative colitis are willing and motivated to try out novice methods of therapy with a high remission potential and which are relatively safe even when their current therapy regime is satisfactory [14, 15].

The spectrum of bacteria is altered in patients with ulcerative colitis compared to healthy individuals. Patients with ulcerative colitis seem to have a lower count of *Bacteroidetes* a *Fermicutes*. Judging my mucosal models these bacteria play an important role in T-cell activation routes.

The first patient was treated by fecal microbiota therapy for ulcerative colitis in 1988, followed by other 55 with different gastrointestinal diseases. Six of those patients followed up with ulcerative colitis remain asymptomatic until this day.

The first study published on non- *Clostridium difficile* infection patients with ulcerative colitis was in 1989 by Bennet and Brinkman, the first patient was Bennet himself who suffered from active colitis for a 7 year period prior to the self-administration of fecal microbiota from a healthy donor, this was followed by a 3 month remission period without the need of any other medication for the first time in all the years of his disease. However evidence of fecal microbiota therapy curing patients with ulcerative colitis is limited to a small group of patients. Why treatment works on some patients and doesn't work on others is yet to be found out. The curing effect of fecal microbiota therapy for ul-cerative colitis is not as immediate as that for *Clostridium difficile* infection, but there are lasting changes in the inflamed mucosa of the gut for better, which in years can cause uninflamed mu-cosa. There are trials currently conducted for the use of fecal microbiota therapy for ulcerative colitis[14, 17, 38–41].

Crohn's disease

Crohn's disease is another common idiopathic bowel disease. The first attempts to treat Crohn's disease with fecal microbiota therapy date back to 1988, however the results are poorly sustained. There are recent studies conducted on this matter with no persuasive histological or clinical effect in the disease progression even with a qualitative change in the microbiota. However anecdotal cases of self-adminstered fecal matter with a positive affect are described [1, 42, 43].

Irritable bowel syndrome

Irritable bowel syndrome is another disease potentially treatable by fecal microbiota transplant. One study was conducted with about 300 patients with an effect in patients with more severe forms of diarrhea and abdominal pain. However, results are nowhere near as dramatic as those with Clostridium difficile infection. There are anecdotal reports of others forms of irritable bowel syndrome such as constipation, however further studies are needed to see a more clear picture [44, 45].

Metabolic syndrome, obesity and energy harvest

In animals and humans microbiota seems to have a direct role in the capability of energy harvest from

food. Germ-free mice are altogether protected from obesity and metabolic syndrome even when a Western diet is rich in fats. However these mice, when colonized with microbiota of normal mice, gain up to 60% body weight in 2 weeks. This is followed by an increase in insulin resistance even after food intake is reduced. Food which originally could not be digested can be fermented and absorbed after inoculation of microbiota. Presence of bacteria in the gut increase hepatic lipogensis via the suppression of certain lipoprotein lipase inhibitors therefore with these observations, the influence on energy homeostasis is suspected.

Some of the fermented metabolites serve as prebiotics for beneficial intestinal bacteria. The reduction of prebiotics and therefore bacteria can cause inflammatory states in the intestine.

Diets rich in fats seem to increase lipopolysacharide containing intestinal microbiota and also downregulate the amount of *Bifidobacteria*. This state is also called metabolic endotoxemia, which is accompanied by a pro-inflammatory state weight gain and insulin resistance. *Bifidobacteria* are capable of lowering levels of lipopolysacharied and normalizing the levels of plasmatic endotoxins, it diminishes metabolic endotoxemia and glucose tolerance can improve, weight loss and increased satiety occurs in human subjects [15, 46].

Short-chain fatty acids such as acetate, butyrate and propionate can be fermented by microbes from undigestable carbohydrates in the human gut. The main short-chain fatty acid in the human gut is acetate, some short-chain fatty acids such as propionate can be used for *de novo* glucose synthesis and can serve as an energy source for the host. Germ-free mice are deficient in short-free fatty acids. After a diet change the composition of the gut microbiota is altered, therefore the availability of certain short-chain fatty acids is also altered. This directly modulates energy absorption, possibly by stimulating peptide YY which is the obesity hormone. The short chain fatty acid with most potential as a stimulating molecule is butyrate, however the precise role of mechanism is unclear. Experiments with mice who were fed with a high-fat western diet supplemented with butyrate did not seem to develop insulin resistance even with obesity[2, 15].

After gastric bypass surgery patients begin losing weight, suggesting that this surgery has a direct effect also followed by an antidiabetic effect which is prior to weight loss itself. Some bacteria like *Faecalibacterium prausnitzii* are less present in obese patients, but seems to increase after this surgery, also the amount of this bacteria negatively correlates with the amount of inflammatory markers where all of this seems to indicate that there is a direct immunomodulating effect of bacteria. Germ-free mice cannot develop diet induced obesity and insulin resistance, this is also shown by the effect of antibiotics on mice with normal microbiota, which have a reduction of adiposity after therapy and an improvement in glucose metabolism [5, 33, 47].

Carbohydrates are the main source of energy for both bacteria and human cells. The human body is not capable of degrading complex plant polysaccharides such as starch, inulin and xylans. The microbiota ferments these into end products like short-chain fatty acids such as acetate, propionate a butyrate. Short chain fatty acids are also an important substrate for inflammation, gut motility, vasodilatation. Also short chain fatty acids are important for nutrition of the colonic epithelium and peripheral tissue. The patterns of fermentation depend on consumed carbohydrates and the microbiota composition.

The only direct proof of energy harvest comes from germfree rats. These rats have reduced amounts of short chain fatty acids in the intestine and twice as much excretion of urinary and fecal calories in comparison with rats on a same diet with the presence of gut microbiota. Germ-free mice must compensate with the increased intake of food. Germ-free mice gain weight within 14 days after being colonized with normal flora. The obesity phenotype is transmissible via microbiota. Rodents colonized with microbiota of obese mice tend to gain twice as much as those colonized by microbiota of lean mice. There are indirect studies which suggest a comparable effect in humans. These is a higher level of ethanol in breath of obese people in comparison to lean people, this suggests, that there is more fermentation to short chain fatty acids and energy harvest processes are more capable in the gut of the obese [48, 49].

Diet directly influenced the composition of the intestinal microbiota, changes in microbiota are noticeable three to four days after a major diet change, but can be readily reversed with the reverse of diet.

It seems that the two main bacteria that are diet-dependent in animal models are *Bacteroidetes* and *Fermicutes*.

In rodent models a high-fat Western diet seems to increase the abundance of *Firmicutes* and decrease the abundance of *Bacteroidetes*. However, there are now no studies that fully prove this in humans.

The microbiota composition depends on the food we consume, people with a higher amount of polysaccharides in their diet, have a higher amount of *Bacteroidetes* in the gut, like the people of rural Africa with mainly *Prevotella* and *Xylanibacter*, on the other hand the people who have a western diet have a higher level of *Enterobacteriaceae*, for example *Shigella* and *Escherichea*.

Prevotella and *Xylanibacter* in the guts of people mainly on a polysaccharide diet, like the children of rural Africa are capable of degrading cellulose a xylans into fecal short chain fatty acids, therefore a maximal amount of energy can be harvested from a fibre rich diet. There are 3 main enterotypes.

The human microbiota can be divided into three main types of enterotype, the division is not 3 discrete entities but more a fluent gradient. Three main bacteria dominate these enterotypes being *Bacteroides*, *Prevotella* and *Ruminococcus*. These three enterotypes are not affected by age, gender or nationality. However all of these are influenced by certain diets. *Enterotypes* dominated by *Bacteroidets* are associated with consumption of a diet dominant in animal proteins and fat, whereas the enterotype dominated by *Prevotella* is associated with a polysaccharide based diet.

The *Ruminococcus* enterotype is least separated and more often merges with the *Bacteroides* enterotype.

However, a 10-day diet change is not enough to change the enterotype of one individual, a long term change is necessary to make a main shift in the microbiota composition to happen.

Specific changes in colonies of bacteria can happen after daily consumption of polysaccharides even after short periods of time. For example, usage of prebiotics such as inulin can induce growth of *Bifidobacterium* species. In obese mice, prebiotics cause a reduction of adiposity and levels of inflammatory molecules derived by bacteria such as some lipopolysacharides in comparison with obese mice who were not fed with prebiotics.

Dietary fat affects microbiota consumption in mice with a reduction of *Bacteroides* and the increase in the number of *Firmicutes* and *Proteobacteria*. The transplantation of microbiota of a high fat diet fed mouse to a germ free recipient increases the adiposity of the recipient mouse significantly. The alteration of microbiota seems to contribute to dietary induced obesity. The precise mechanism is not known [4, 5, 18, 50].

Anecdotal cases of fecal microbiotia therapy being applied to patients with multiple sclerosis, Parkinson's disease, chronic fatigue syndrome, idiopathic thrombocytopenic purpura, rheumatoid arthritis sacroileitis, kalitosis, acne, insomnia, depression have been described in literature. A positive effect was observed in all cases.

The intestine with its immune system and microbial ecosystem plays a crucial role in the human body. Different insults can alter this subtle balance leading to a disease which can be life threatening. It is certain that fecal microbiota therapy is an important and rising method of therapy in the last few years, and will be even more so in the years to come. More studies on the precise mechanisms of action of this therapy and the composition of micobiota must be completed so that the therapy can be under-stood and preferably one day personalized for the exact need of every patient. Also a more standardized guideline for the composition of the fecal matter and the route of administration and the preparation of the host and donor is needed worldwide to make this promising and inspiring method of treatment more standardized.

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