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Review

Fecal Microbiota Transplantation: Impacts on Neurological Disorders, Allergies, and Cancer

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ABSTRACT

Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy, fecal transfusion, and stool transplantation, is considered to be one of the remarkable treatments of the last century. Fecal microbiota transplantation is the process of filtering and diluting the stool from a healthy donor and placing it in the gastrointestinal tract of the recipient. It was first used orally in the fourth century, under the name of "Yellow Soup" in China for food poisoning and diarrhea. Recently, it has been widely used in various clinical situations, recurrent and resistant cases of Clostridium difficile bacterial infection. The purpose of the FMT procedure is to improve the intestinal flora by suppressing the deteriorated intestinal microbiota with a healthy bacterial community. In this review, how to treat diseases with FMT and the positive effects of this method on patients with neurological disorders, allergy and cancer were discussed.

Keywords: Clostridium difficile, depression, fecal microbiota transplantation, neurological disorders

The gastrointestinal system includes several bacteria types that help digestion, facilitate maturation of colon epithelium, and have protection from pathogens function. These bacteria called intestinal microbiomes vary following the developmental processes of individuals. In addition, its composition may change with changes in diet, probiotics, prebiotics, viruses, and antibiotics, as well as environmental factors such as drugs. Various types of disease groups, including infectious diseases (infectious gastroenteritis, Clostridium difficile infection (CDI), autoimmune diseases (allergic disease, diabetes, inflammatory bowel disease), some general health problems (obesity, functional disorders), and psychiatric diseases, it is associated with the gut microbiota.[1-4] In recent years, various medical treatment methods have been begun to be used to ameliorate intestinal disorders. However, except for fecal microbiota transplantation (FMT), many of them do not offer satisfactory clinical results in ameliorating the microbiota. Fecal microbiota transplantation, or stool transplantation, is a method for placing stool from a healthy donor in the gastrointestinal tract of another patient and normalizing and treating the recipient's gut microbiota composition.[5,6] The first application of FMT in the world started with a Chinese doctor in the fourth century, when people with severe diarrhea made them drink a fecal suspension, which he called yellow soup.[7] Fecal microbiota transplantation was first applied to 30 ulcerative colitis patients who were resistant to medical treatment by Uygun et al.[8] in 2015 in Turkey. After FMT application, 70% clinical improvement and 43.3% complete recovery (clinical, laboratory, and endoscopic) were achieved. The use of FMT therapy is increasing day by day from infectious diseases to chronic diseases. In addition, new insights linking the gut microbiota to non-intestinal diseases continue to further expand the treatment of FMT.[9]

The fecal microbiota transplantation process implemented increasingly has been preferred since it increases the success of therapy and the life quality of patients and decreases the cost of therapy. It has been mostly used in the treatment of CDI in recent years. While the success of recurrent CDI

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with antimicrobial treatment is 30%, it increases to 80-90% with FMT.[10-13] In addition, studies are showing that it can be adopted as a useful primary treatment in inflammatory bowel diseases (such as ulcerative colon, Crohn's disease).[14-17] It has also been shown that bowel movements are reduced in irritable bowel yndrome.[18] Apart from intestinal diseases, the therapeutic effect of FMT has also been demonstrated in obesity, diabetes,[19,20] multiple sclerosis, idiopathic thrombocytopenic purpura, autism, resistant infections, Parkinson's disease,[21] and multiple organ failure.[9]

The conditions to be considered in FMT donor selection are given below. Apart from all these, the donor's stool; CDI should be examined for toxin and Cryptosporidium, Helicobacter pylori, Yersinia, Campylobacter, Shigella, Salmonella, Enteropathogenic Escherichia coli antigens, Rotavirus, Adenovirus, Enterovirus, Parechovirus, Sapoviruses, Noroviruses, Astroviruses, and Giardia parasites. In addition, the donor's blood should be counted, liver function tests, human immunodeficiency virus (HIV)-1 and 2 antibodies, Human T-Lymphocytic virus, Hepatitis A, B and C viruses, Cytomegalovirus and Epstein Barr virus, Strongyloides, Amebiasis, Syphilis should be screened. Beta-subunit of human chorionic gonadotropin test should be performed to rule out the suspicion of pregnancy in female patients.[9, 22-26]

There are four points to consider in donor selection such as inclusion criteria, exclusion criteria, factors that affect gut microbiota composition, and other situations. Those who are between the ages of 18 and 65, have no history of gastrointestinal disease or current symptoms and have not taken antimicrobial medications or drugs other than probiotics that can modify their bowel motions in the last three months belong to the inclusion criteria. Exclusion criteria include infectious agents such as HIV, Hepatitis B, or C, having been exposed to HIV or viral hepatitis in the previous 12 months, using illegal drugs, having a tattoo or body piercing within six months, engaging in high-risk sexual behavior, having a known current infectious disease, risk factors for variant Creutzfeldt-Jakob disease, and gastrointestinal comorbidities, existing gastrointestinal malignancy or known history of polyps, or having a strong family. Taking antimicrobials (antibiotics, antifungals, antivirals) or probiotics and a proton pump inhibitor in the previous three months, taking major immunosuppressive drugs, receiving systemic antineoplastic agents, and living with people with active gastrointestinal infections at home are all factors that influence gut microbiota composition. Other situations include systemic autoimmunity (eg multiple sclerosis, connective tissue disease), atopic disease, food allergy, metabolic syndrome, obesity (body mass index>30) or moderate to severe malnutrition/malnutrition, chronic pain syndromes or neurodevelopmental disorders, history of malignant disease or ongoing oncological treatment, long term imprisonment, and having a body piercing or tattoo six months ago.[11,23, 27]

FECAL MICROBIOTA TRANSPLANTATION

The colonoscopy method has been mostly preferred in transferring fecal material obtained from donor to recipient. In addition to this method, nasogastric tube, nasoduodenal tube, gastroscopy, jejunoscopy, retention enema, and oral capsule methods are used.[6,9,23] Regardless of the method of application of fecal material, the material must remain in the intestinal lumen for at least four hours, if possible for six to eight hours, for the transplantation to be effective.[9, 23, 27] The appropriate amount of fecal material is given to the recipient in the left lateral position according to the method used and the tolerance status of the patient. The application should be done by an experienced specialist and by protecting the applied area against the risk of trauma. Special consideration should be given to patients with a history of fissures or hemorrhoids. The decision to continue or stop the infusion should be guided by the patient's wishes against the emergency.[5, 23,27]

Fecal microbiota transplantation is generally regarded safe, with a minor, major, or possible adverse events being the most common side effects. Minor side effects can be loss of bowel moments, constipation, nausea, vomiting, transient fever, or abdominal cramps and pain. Examples of major side effects include aspiration pneumonia, septic shock, death in over-application, several infections with the transmission of enteric pathogens, and other problems related to the procedure and anesthesia. There are also possible side effects such as the transmission of infectious organisms that are not yet known to cause disease years later (e.g. HIV, hepatitis C) and changes in the gut flora. These changes can trigger chronic illnesses including obesity, diabetes, atherosclerosis, inflammatory bowel disease, colon cancer, liver disease, irritable bowel syndrome, asthma, and autism.[5,9,12,27]

CLOSTRIDIUM DIFFICILE INFECTION AND FECAL MICROBIOTA TRANSPLANTATION

Clostridium difficile infection is known to be an increasingly common disease in developed countries, characterized by marked diarrhea associated with overgrowth of toxigenic Clostridium difficile strains in the colon. While the case of CDI was 98 thousand in 1996 in the USA, it is between five thousand and three million today.[28] Institutions such as the European Society for Clinical Microbiology and Infectious Diseases, American Gastroenterology, and the American Food and Drug Administration recommend FMT as a treatment option for recurrent CDI. The success rate in the treatment of recurrent CDI was found to be 92%.[29] It has been reported that the success rate of FMT treatment applied after CDI exposure is 76% and there is no difference between genders. While FMT via enema gave a positive response in 74%, FMT via nasoenteric tube provided 80% success.[28] The application of FMT delivered via the nasoduodenal route was evaluated as superior to the standard oral vancomycin applied in the treatment of CDI.[30] It is thought that FMT allows the increase of secondary bile acids and short-chain fatty acids, which play an inhibitory role in the development of Clostridium difficile, and is therefore effective in the treatment of CDI.[31]

EFFECTS OF FECAL MICROBIOTA TRANSPLANTATION ON BODY WEIGHT CHANGES

It is known that dysbiosis, which develops as a result of the imbalance in the microbiota, promotes triglyceride synthesis in the liver by increasing energy efficiency with the fermentation of indigestible polysaccharides. It is thought that dysbiosis also leads to fat storage in adipocytes by increasing the activity of lipoprotein lipase and therefore indirectly contributes to obesity.[32, 33] It has been determined that FMT affects weight change. A 60% increase in adiposity and significant insulin resistance development was observed in 14 days when FMT was applied to germ-free mice with restricted food consumption from normal mice.[33] In a study examining the effect of the obese microbiome transplanted with FMT, energy harvesting capacity from the diet and body fat tissue were increased. With donor selection with an obese microbiome, significant weight gain was observed in non-obese individuals prior to administration. Therefore, the selection of obese/overweight donors is not recommended for FMT.[34] Another hypothesis developed on this practice is that calories from food consumed may increase to varying degrees by certain organisms' production of short-chain fatty acids from indigestible carbohydrates. In this way, it can be applied in the treatment of anorexia nervosa by contributing to weight gain by pointing to increased energy intake despite stable diet intake.[35]

THE EFFECTS OF FECAL MICROBIOTA TRANSPLANTATION ON CARDIOMETABOLISM

Myocarditis is defined as an inflammatory disease of the heart muscle. Considering the etiology, drugs, toxic substances, viruses, bacteria, protozoa, and worms have an important place.[36] It is known that dysbiosis is effective in heart diseases as well as in various diseases. In addition, intestinal-derived endotoxic trimethylamine N-oxide, which increases with the consumption of choline, L-carnitine, and phosphatidylcholine, has been associated with heart diseases such as atherosclerosis.[37] Recently, FMT has been tested in the treatment of cardiometabolic diseases. In a study controlling the effectiveness of FMT application, it was observed that the Firmicutes/Bacteroidetes ratio and necrotic area decreased by 10% as a result of restoration in the gut microbiota on the 21st day after FMT was applied to mice with autoimmune myocarditis.[38] In dogs diagnosed with parvoviral enteritis, which is an infectious viral disease and progressing with acute myocarditis, a significant improvement was observed within 48 hours with the FMT procedure.[39] In the light of these positive results, more studies are needed to determine the effectiveness of FMT in the treatment of cardiometabolic diseases.

INSULIN RESISTANCE AND FECAL MICROBIOTA TRANSPLANTATION

Insulin resistance is defined as a decreased response to insulin, even to an acceptable level of normal insulin, by decreasing sensitivity to insulin.[40,41] The basic mechanism of insulin resistance is considered to be a defect in insulin activity.[42] The relationship of gut microbiota with insulin resistance is based on dysbiosis.[43] Dysbiosis has been found with an increase in Clostridium coccoides and Atopobium cluster species in the intestines of individuals with type 2 diabetes.[44] Pharmaceuticals that cause dysbiosis are also known to cause insulin resistance and glucose intolerance.[43] The role of calorie-free artificial sweeteners in the microbiota has

been shown to develop dysbiosis and cause glucose intolerance by creating changes in short-chain fatty acids.[45] An increase in peripheral and hepatic insulin sensitivity was observed after infusion of allogeneic microbiota administered to individuals with metabolic syndrome. This situation is based on the increased butyrate production with the increase in microbial diversity. Butyrate contributes to insulin sensitivity by reducing the translocation of endotoxic components in the gut.[46] Fecal microbiota transplantation was applied to 18 individuals with metabolic syndrome and a significant increase in insulin sensitivity was observed in nine individuals.[34] In a study examining the efficacy and safety of oral FMT capsules in obese individuals, a non-significant increase in insulin sensitivity was found after administration. The use of oral FMT capsules has been considered safe in obese individuals.[47]

FECAL MICROBIOTA TRANSPLANTATION IN NEUROLOGICAL DISORDERS

All microorganisms in the gastrointestinal tract affect pathways such as the immune system, direct neuronal communication, and hormonal signal transmission. Metabolites such as gamma-aminobutyric acid (GABA) and serotonin produced by these microorganisms form the basis of the brain-intestinal axis. The interaction of the microbiota with the central nervous system is mainly the metabolites produced by the enteric nervous system, vagus nerve, immune system, and host microorganisms. It has been emphasized that leaky gut stimulated by dysbiosis can cause neurological diseases with this axis pathway.[48,49] Attention is drawn to the presence of neurological changes as a result of infection by pathogenic agents. Behavioral disorders were detected in mice infected with Toxoplasma gondii, and it was pointed out that the cause of abnormal behavior in humans could be various infections[50]. While there was a 26% decrease in fecal Streptococcus species, a 5% increase was found in Bifidobacteria species.[51] Amyloid and Tau protein pathology in the brain was reduced after FMT was administered to mice experiencing Alzheimer's-like symptoms.[52] An increase in cognition and a decrease in systemic inflammation have been reported with this change.[53,54]

AUTISM SPECTRUM DISORDER AND FECAL MICROBIOTA TRANSPLANTATION

Autism is known as a severe neurodevelopmental disorder affecting social communication and behavior characterized by various complications in the immune mechanism and gastrointestinal system. Since the intestinal microbiota is related to the immune mechanism and the gastrointestinal system, attention has been drawn recently to the relationship between dysbiosis developing in the intestine and autism.[55] It has been determined that Clostridial species are more common in the intestinal microbiota of children with autism.[56] In individuals with autism, the component of the gut microbiota has been associated with gastrointestinal symptoms that develop with autism severity. In this context, it was observed that bacterial diversity, especially in Bifidobacterium, Prevotella, Desulfovibrio species, increased at the end of FMT applied to children diagnosed with autism. A reduction of 80% was observed in gastrointestinal symptoms, and this continued for eight weeks.[57] In a study evaluating the FMT procedure applied to five children with autism, it was reported that symptoms disappeared in only two children after the application.[58] A decrease in symptom severity, social impairment, problem behaviors, and cerebral oxidative stress is observed in autism after FMT.[59] In addition to many factors in autism, the effect of the intestinal microbiota is based on the negative course of microbial metabolites from the mother's womb. In samples from individuals with autism, overproduction of short-chain fatty acids that respond to the abnormal gut microbiome and abnormality of metabolites such as para-cresol and ammonia have been observed.[60]

PARKINSON'S DISEASE AND FECAL MICROBIOTA TRANSPLANTATION

Various environmental factors such as caffeine and smoking, head trauma, age, gender, heavy metals, and pesticide-type components are important factors for Parkinson's disease.[61-63] Bidirectional communication in the brain-gut axis can also cause Parkinson's symptoms. This situation draws attention to the role of intestinal involvement in Parkinson's disease.[64,65] The basic mechanism here is that metabolites obtained from the gut microbiota affect immune cells that reach the brain via the brain-intestinal axis. Progressive exposure with affected immune cells causes dysfunction of dopaminergic neurons and leads to Parkinson's disease.[66] In addition to the brain-intestinal axis, the main factor in Parkinson's disease was a decrease in Prevotellaceae species and a significant increase in Enterobacteriaceae species, leaky gut, and increased permeability due to these changes were reported.[67] With FMT applied to mice

with Parkinson's, a decrease in dysbiosis and physical disorders, an increase in dopamine and serotonin were observed. Activation of microglia and astrocytes in the substantia nigra and decreased expression of toll-like receptor 4/tumor necrosis factor-α in the brain and intestine were observed. It has been emphasized that this way, neuroinflammation can be suppressed and Parkinson's patients can be protected.[68] In the diagnosis of Parkinson's disease, an increase in dopaminergic neurons and a decrease in motor symptoms are observed after FMT.[59, 69]

EPILEPSY AND FECAL MICROBIOTA TRANSPLANTATION

Epilepsy is a condition that develops with excessive and sudden electrical discharges of brain cells characterized by seizures, fainting and bruising.[70] Intestinal microbiota influences the brain with mediators such as gut bacteria, blood-brain barrier, hypothalamic-pituitary-adrenal axis, brain-intestinal axis, immune system, and intestinal mucosa. Cognitive function and behaviors can be affected in these ways. Noticeable differences in epilepsy patients were determined, and the effective rate of microbiota in epilepsy is known to be 60%.[71,72] When the microbiota of epilepsy patients was examined, it was found that Proteobacteria phylum species were higher, Firmicutes, Bacteroidetes and Actinobacteria species were less than the control group.[73] A significant decrease in Proteobacteria species and an increase in Bacteroides, Prevotella, and Bifidobacterium species were found with the ketogenic diet applied in the treatment of epilepsy.[74] After FMT application in epilepsy, a decrease in the proconvulsant effect of stress, an increase in seizure threshold, and a decrease in seizure frequency are observed.[59] In a case study with a history of epilepsy with Crohn's disease, behavioral symptoms improved, and epileptic seizures decreased after FMT administration. The effectiveness of FMT treatment in the prevention of epileptic seizures has been emphasized by discontinuing the use of antiepileptic drugs. In the study, it was revealed that it can contribute to the treatment of epilepsy by renewing the gut microbiota by drawing attention to the brain-intestinal effect.[75]

ISCHEMIC STROKE AND FECAL MICROBIOTA TRANSPLANTATION

Stroke was defined as a disorder that develops suddenly in the brain functions for no reason except vascular reasons.[76] It is known that cerebral ischemic stroke causes a decrease in short-chain fatty acids, despite the fact that an increase in gut permeability by creating dysfunctional gut microbiota.[77] In an experimental study, it was observed that the permeability of the intestine decreased with increasing short-chain fatty acids at the end of the application of a microbially rich FMT process, and this decrease treated ischemic stroke through the food-intestinal axis. The highest negative correlation was found with butyric acid in ischemic stroke. The intestinal repair function of butyric acid has been associated with an increase in Lactobacillus species.[77] An increase in Lactobacillus species reduces the risk of stroke by decreasing cerebral infarction volume, oxidative stress, and apoptosis of neural cells. It also prevents barrier dysfunction by repairing intestinal epithelial cells.[78] Microbiota obtained from old mice were implanted with FMT in young mice after stroke, an increase in the Firmicutes/Bacteroidetes ratio, a decrease in physical performance, and an improvement after stroke were found.[79] It has been observed that proinflammatory T cells are induced in the ischemic brain and intestinal immune compartment after colonization with the dysbiotic microbiome. It has been pointed out that FMT can be used in the treatment of stroke by reducing the dysbiosis that develops as a result of brain lesions.[80]

ATAXIA AND FECAL MICROBIOTA TRANSPLANTATION

Ataxia is known as a neurodegenerative disorder characterized by impaired walking, balancing, and speech activities that require coordination.[81] Changes in gut flora can affect the brain and brain-gut axis by modulating the nervous system. In a study investigating the relationship between intestinal microbiota and acute cerebellar ataxia, it was found that children diagnosed with acute cerebellar ataxia underwent intestinal surgery. Paraeggerthella, Rothia, Candidatus Saccharibacteria species decreased in patients with a history of surgery, but an increase was observed in Acetivibrio, Catenibacterium, and Comamonas species.[82] The microbial diversity provided by FMT and the destruction of leaky gut is associated with the prevention of dysbiosis and the provision of aerobiosis. In an experimental study investigating the efficacy of FMT in ataxia, it was observed that ataxic symptoms disappeared completely, head tilting disappeared, and walking without support was achieved with FMT application.[83]

DEPRESSION AND FECAL MICROBIOTA TRANSPLANTATION

In the gut microbiota, the dysbiosis state can change the activity of the hypothalamic-pituitary-adrenal axis, modify the balance of brain-derived neurotrophic factors, increase intestinal permeability, release monoamine neurotransmitters and systemic inflammation. These changes can contribute to the development of depression.[84] It has been reported that there is a negative correlation between Bacteroides, Parabacteroidetes, and Escherichia species, which are defined as sources of GABA, and depression.[85] In a case report, a geriatric patient with depression was excluded from antidepressants and FMT was administered from his grandchild. While there was a decrease in Bacteroidetes species after application, a significant increase was observed in Firmicutes species. It has been observed that less sleepiness, better appetite, and talkativeness develop.[86] It has been determined that FMT application in patients with irritable bowel syndrome provides microbial improvement and thus there is a significant decrease in anxiety and depression scores of individuals.[87]

ASTHMA AND FECAL MICROBIOTA TRANSPLANTATION

Asthma is known as a chronic inflammatory disease that develops with shortness of breath, wheezing, cough, chest pain.[88] In addition to various environmental factors, it has been pointed out that exposures related to asthma in humans may increase with the changing microbiota with conditions such as cesarean delivery, urban life, antibiotic use and not being able to breastfeed.[89] Intestinal microbiota plays a role as the most important postnatal source of the immune system in the formation and control of the immune response in early childhood. Recently, oral intake of probiotics and prebiotics have been emphasized in the treatment of asthma, but it is stated that FMT treatment is superior because probiotics temporarily colonize the intestinal lumen.[90] An alternative treatment with Mycobacterium vaccae has been suggested for patients with allergic disorders. It has been shown that taking Mycobacterium vaccae via FMT contributes to the reduction of symptoms of allergic airway disease.[91] Lachnospira, Veillonella, Faecalibacterium, and Rothia bacteria are significantly less in children at risk for asthma. It has been determined that the experimental application of these bacterial taxa with FMT prevents the development of asthma.[92, 93]

FOOD ALLERGY AND FECAL MICROBIOTA TRANSPLANTATION

Food allergy is known as an extreme reaction to foods through defense mechanisms. These reactions develop immunologically. Basophils of the intestinal microbiota may develop a susceptibility to food allergy by affecting the function of the intestinal barrier and modulation of type II immunity. In a study examining microbial changes in early food allergy, higher Lactobacilli, and lower Enterobacteria, Bifidobacteria were found in infants with milk allergy.[94,95] No response to food antigens was observed in germ-free mice saturated with Escherichia coli and Lactobacilli species.[96] In another study, saturation with Anaerostipes caccae reduced allergic symptoms in a mouse model of food allergy. Attention is drawn to the treatment approaches performed with target bacteria in food allergies.[97] Fecal microbiota transplantation has been seen as a promising treatment in this field. Post-exposure anaphylaxis could be prevented with an FMT procedure performed on a mouse model with a food allergy from a healthy infant. At the same time, treatment with Clostridiales species contributed to the prevention of food allergy in mice.[98]

CANCER AND FECAL MICROBIOTA TRANSPLANTATION

Considering the causes of cancer development, it is known that 20% of them are infected agents.[99] It has been reported that there is an increase in Fusobacterium, Porphyromonas, Peptostreptococcus, Parvimonas, and Enterobacter species in colorectal cancers.[100] In a recent study, Fusobacterium, Bacteroides, and Streptococcus species were found to be high in colorectal cancer. Basically, the knowledge that there is an increase in pathogen types in cancer types or a decrease in beneficial bacteria leads to the consideration of FMT as a treatment.[101] It is stated that the application of FMT before anticancer treatment can further increase the effectiveness of monotherapy and reduce tumor resistance.[102] It is thought that the place of FMT application in cancer treatment will become clear with comprehensive studies to be conducted in the coming years.

SIDE EFFECTS OF FECAL MICROBIOTA TRANSPLANTATION APPLICATIONS

Although short-term follow-up of the application with a complex microbiota relationship is available,

its long-term reliability has not yet been determined. Anticipated short-term side effects; gastrointestinal symptoms such as abdominal discomfort, diarrhea, transient fever, vomiting, as well as serious events such as pneumonia, inflammatory bowel disease attack, exacerbation of chronic diseases, and death due to weakened immunity. It can be said that the long-term effects of infection-related complications and the formation of chronic diseases.[103]

In conclusion, FMT is a new promising treatment practice in diseases that do not respond to various medical treatments and become chronic. Although it is effective in the gastrointestinal system and non-gastrointestinal diseases, it is accepted by some scientists, but it is a treatment attempt that some people hesitate due to its negative effects. The role of this practice, which has been the subject of various studies, in various diseases of unknown pathogenesis will only be understood as we get to know the gastrointestinal microbiota better. Compared to other treatment methods, the preparation of mixtures containing individual components based on the needs of the individual, the choice of delivery route, and donor are the positive aspects of the application, but many individual side effects are also seen. The most important limitation of the application is the small number of acceptable randomized controlled studies and the short follow-up period. Lack of long-term follow-up may raise doubts about the reliability of the application. More studies are needed to determine the complete safety of the treatment.

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REFERENCES

1. Matsuoka K, Mizuno S, Hayashi A, Hisamatsu T, Naganuma M, Kanai T. Fecal microbiota transplantation for gastrointestinal diseases. The Keio Journal of Medicine 2014;63:69-74.
2. Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. Therapeutic Advances in Gastroenterology 2013;6:295-308.
3. Icaza-Chávez ME. Gut microbiota in health and disease. Revista de Gastroenterología de México (English Edition) 2013;78:240-8.
4. Duncan SH, Louis P, Flint HJ. Cultivable bacterial diversity from the human colon. Letters in Applied Microbiology 2007;44:343-50.
5. Gupta A, Khanna S. Fecal microbiota transplantation. The Journal of the American Medical Association 2017;318:102.
6. Rossen NG, MacDonald JK, de Vries EM,D'Haens GR, de Vos WM, Zoetendal EG, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World Journal of Gastroenterology 2015;21:5359-71.
7. Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? The American Journal of Gastroenterology 2012;107:1755
8. Uygun A, Ozturk K, Demirci H, Oger C, Avci IY, Turker T, et al. Fecal microbiota transplantation is a rescue treatment modality for refractory ulcerative colitis. Medicine 2017;96: e6479.
9. Wang J-W, Kuo C-H, Kuo F-C, Wang Y-K, Hsu W-H, Yu F-J, et al. Fecal microbiota transplantation: Review and update. Journal of the Formosan Medical Association 2019;118(Supplement 1);23-31.
10. Samuel BP, Crumb TL, LaVigne HD. Nursing assessment for "do it yourself" fecal microbiota transplantation. Gastroenterology Nursing 2016;39:60-2
11. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for clostridium difficile ınfection: systematic review and meta-analysis.The American Journal of Gastroenterology 2013;108:500-8.
12. Boyle ML, Ruth-Sahd LA, Zhou Z. Fecal microbiota transplant to treat recurrent Clostridium difficile infections. Critical Care Nurse 2015;35:51-64.
13. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S,Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent clostridium difficile. New England Journal of Medicine 2013;368:407-15.
14. Kunde S, Pham A, Bonczyk S, Crumb T, Duba M, Conrad HJ, et al. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. Journal of Pediatric Gastroenterology and Nutrition 2013;56:597-601.
15. Kao D, Hotte N, Gillevet P, Madsen K. Fecal microbiota transplantation ınducing remission in crohn's colitis and the associated changes in fecal microbial profile. Journal of Clinical Gastroenterology 2014;48:625-8.
16. Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, et al.Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomized placebo-controlled trial. The Lancet 2017;389:1218-28.
17. Bafeta A, Yavchitz A, Riveros C, Batista R, Ravaud P. Methods and reporting studies assessing fecal microbiota transplantation: A systematic review. Annals of Internal Medicine 2017;167:34-9.
18. Tian H, Ding C, Gong J, Ge X, McFarland LV, Gu L, et al. Treatment of slow transit constipation with fecal microbiota transplantation: A pilot study. Journal of Clinical Gastroenterology 2016;50:865-70.
19. Erbas O, Pala HG, Pala EE, Oltulu F, Aktug H, Yavasoglu

A, Taskiran D. Ovarian failure in a diabetic rat model: nuclear factor-kappaB, oxidative stress, and pentraxin-3. Taiwanese Journal of Obstetrics and Gynecology. 2014 Dec 1;53:498-503.

20. Elmas O, Erbas O, Yigitturk G. The efficacy of Aesculus hippocastanum seeds on diabetic nephropathy in a streptozotocin-induced diabetic rat model. Biomedicine & Pharmacotherapy. 2016 Oct 1;83:392-6.
21. AL O, EX F, RIMENTAL P, BASIC ME, IEN S. Effects of Green Tea Polyphenols and Oxidative Stress on Alzheimer's and Parkinson's Diseases. Journal of Experimental and Basic Medical Sciences. 2021;2:1-6.
22. Huang Y, Wang X, Li X, Peng N. Successful fecal bacteria transplantation and nurse management for a patient with ıntractable functional constipation: A case study. Holistic Nursing Practice 2016;30:116-21.
23. Uygun A. Fekal Mikrobiyota transplantasyonu (FMT). Journal of Biotechnology and Strategic Health Research 2017;1(Special Issue):132-40.
24. Demirci H, Uygun A. Fekal transplantasyon nasıl ve kime uygulanmalı? Güncel Gastroenteroloji 2014;18:444-7.
25. Samuel BP, Crumb TL, Duba MM. What nurses need to know about fecal microbiota
transplantation: Education, assessment, and care for children and young adults. Journal of Pediatric Nursing: Nursing Care of Children and Families 2014;29:354-61.
26. Link A, Lachmund T, Schulz C, Weigt J, Malfertheiner P. Endoscopic peroral jejunal fecal microbiota transplantation. Digestive and Liver Disease 2016;48:1336-9.
27. Leis S, Borody TJ, Jiang C, Campbell J. Fecal microbiota transplantation: A 'how-to' guide for nurses. Collegian 2015;22:445-51.
28. Stebel R, Vojtilova L, Svacinka R, Husa P. Faecal microbiota transplantation in the treatment of Clostridioides difficile infection. Human Microbiome Journal. 2020;100070:16.
29. Kim KO, Gluck M. Fecal Microbiota Transplantation: An Update on Clinical Practice. Clin Endosc. 2019 Mar;52:137-43.
30. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013 Jan 31;368:407-15.
31. Weingarten AR, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. Gut Microbes. 2017 May 4;8:238-52.
32. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004 Nov 2;101:15718-23.
33. Bozkurt H, Özer S, Yılmaz R, Sönmezgöz E, Kazancı Ö, Erbaş O, et al. Assessment of neurocognitive functions in children and adolescents with obesity. Applied Neuropsychology: Child. 2017 Oct 2;6:262-8.
34. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006 Dec 21;444:1027-31.
35. de Clercq NC, Frissen MN, Davids M, Groen AK, Nieuwdorp M. Weight Gain after Fecal Microbiota Transplantation in a Patient with Recurrent Underweight following Clinical Recovery from Anorexia Nervosa. Psychother Psychosom. 2019;88:58-60.
36. Feldman AM, McNamara D. Myocarditis. N Engl J Med. 2000 Nov 9;343(19):1388-98.
37. Tang WH, Hazen SL. The Gut Microbiome and Its Role in Cardiovascular Diseases. Circulation. 2017 Mar 14;135:1008-10.
38. Hu XF, Zhang WY, Wen Q, Chen WJ, Wang ZM, Chen J, et al. Fecal microbiota transplantation alleviates myocardial damage in myocarditis by restoring the microbiota composition. Pharmacol Res. 2019 Jan;139:412-21.
39. Pereira GQ, Gomes LA, Santos IS, Alfieri AF, Weese JS, Costa MC. Fecal microbiota transplantation in puppies with canine parvovirus infection. J Vet Intern Med. 2018 Mar;32:707-11.
40. Flier JS. Lilly Lecture: syndromes of insulin resistance. From patient to gene and back again. Diabetes. 1992 Sep;41:1207-19.
41. Erbas O, Taşkıran D, Oltulu F, Yavaşoğlu A, Bora S, Bilge O, et al. Oxytocin provides protection against diabetic polyneuropathy in rats. Neurological research. 2017 Jan 2;39:45-53.
42. Consensus Development Conference on Insulin Resistance. 5-6 November 1997. American Diabetes Association. Diabetes Care. 1998 Feb;21:310-4.
43. Velmurugan G, Ramprasath T, Gilles M, Swaminathan K, Ramasamy S. Gut Microbiota, Endocrine-Disrupting Chemicals, and the Diabetes Epidemic. Trends Endocrinol Metab. 2017 Aug;28:612-25.
44. Sato J, Kanazawa A, Ikeda F, Yoshihara T, Goto H, Abe H, et al. Gut dysbiosis and detection of "live gut bacteria" in the blood of Japanese patients with type 2 diabetes. Diabetes Care. 2014 Aug;37:2343-50.
45. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014 Oct 9;514:181-6.
46. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012 Oct;143:913-6.e7.
47. Yu EW, Gao L, Stastka P, Cheney MC, Mahabamunuge J, Torres Soto M, et al. Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial. PLoS Med. 2020 Mar 9;17:e1003051.
48. Evrensel A, Ceylan ME. Bağırsak Beyin Ekseni: Psikiyatrik Bozukluklarda Bağırsak Mikrobiyotasının Rolü. Current Approaches in Psychiatry/Psikiyatride Guncel Yaklasimlar. 2015;7:461-72.
49. Rodenbach R, Kavalieratos D, Tamber A, Tapper C, Resick J, Arnold R, et al. Coaching Palliative Care Conversations: Evaluating the Impact on Resident Preparedness and Goals-of-Care Conversations. J Palliat Med. 2020

Feb;23:220-5.
50. Flegr J. Influence of latent Toxoplasma infection on human personality, physiology and morphology: pros and cons of the Toxoplasma-human model in studying the manipulation hypothesis. J Exp Biol. 2013 Jan 1;216(Pt 1):127-33.
51. Thurm T, Ablin JN, Buskila D, Maharshak N. Fecal Microbiota Transplantation for Fibromyalgia: A Case Report and Review of the Literature. Open Journal of Gastroenterology. 2017;7:131-9.
52. Cevik B, Solmaz V, Yigitturk G, Cavusoğlu T, Peker G, Erbas O. Neuroprotective effects of erythropoietin on Alzheimer's dementia model in rats. Advances in Clinical and Experimental Medicine. 2017;26:23-9.
53. Sun J, Xu J, Ling Y, Wang F, Gong T, Yang C, et al. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl Psychiatry. 2019 Aug 5;9:189.
54. Erbaş O, Erdoğan MA, Khalilnezhad A, Solmaz V, Gürkan FT, Yiğittürk G, et al. Evaluation of long-term effects of artificial sweeteners on rat brain: A biochemical, behavioral, and histological study. Journal of biochemical and molecular toxicology. 2018 Jun;32:e22053.
55. Vuong HE, Hsiao EY. Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. Biol Psychiatry. 2017 Mar 1;81:411-23.
56. Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, et al. Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. 2002 Sep 1;35(Suppl 1): S6-S16.
57. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017 Jan 23;5:10.
58. Aroniadis OC, Brandt LJ. Fecal microbiota transplantation: past, present, and future. Curr Opin Gastroenterol. 2013 Jan;29:79-84.
59. Vendrik KEW, Ooijevaar RE, de Jong PRC, Laman JD, van Oosten BW, van Hilten JJ, et al. Fecal Microbiota Transplantation in Neurological Disorders. Front Cell Infect Microbiol. 2020 Mar 24;10:98.
60. Yang Y, Tian J, Yang B. Targeting gut microbiome: A novel and potential therapy for autism. Life Sci. 2018 Feb 1;194:111-9.
61. Kieburtz K, Wunderle KB. Parkinson's disease: evidence for environmental risk factors. Mov Disord. 2013 Jan;28:8-13.
62. Aksoy D, Solmaz V, Çavuşoğlu T, Meral A, Ateş U, Erbaş O. Neuroprotective effects of eexenatide in a rotenone-induced rat model of Parkinson's disease. The American Journal of the Medical Sciences. 2017 Sep 1;354:319-24.
63. Ünal B, Altuntaş İ, Erbaş O. Parkinson's Disease: Mechanisms, Pathogenesis, Animal Models and Tests. Journal of Experimental and Basic Medical Sciences. 2020;1:135-9.
64. Perez-Pardo P, Dodiya HB, Broersen LM, Douna H, van Wijk N, Lopes da Silva S, et al. Gut-brain and brain-gut axis in Parkinson's disease models: Effects of a uridine and fish oil diet. Nutr Neurosci. 2018 Jul;21:391-402.
65. Erbaş O, Yılmaz M, Taşkıran D. Levetiracetam attenuates rotenone-induced toxicity: A rat model of Parkinson's disease. Environmental Toxicology and Pharmacology. 2016 Mar 1;42:226-30.
66. Chen Q, Wang L, Hong S, Chen, Y. Integrated Design of JSCC Scheme based on Double Protograph LDPC Codes System. IEEE Communications Letters. 2018;23:218-21.
67. Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord. 2015 Mar;30:350-8.
68. Sun MF, Zhu YL, Zhou ZL, Jia XB, Xu YD, Yang Q, et al. Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: Gut microbiota, glial reaction, and TLR4/TNF-α signaling pathway. Brain Behav Immun. 2018 May;70:48-60.
69. Erbas O, Oltulu F, Taskiran D. Suppression of exaggerated neuronal oscillations by oxytocin in a rat model of Parkinson's disease. Gen Physiol Biophys. 2013 Dec 1;32:517-25.
70. Aktekin B, Ağan K, Arman F, Aslan K, Aykutlu E, Baklan B, et al. Epilepsi Rehberi. Türk Nöroloji Epilepsi Çalışma Grubu. Epilepsi 2012;18:26-38
71. World Health Organization. Epilepsy 15.09.2020. Available from: https://www.who.int/news-room/fact-sheets/detail/epilepsy
72. Wu J, Zhang Y, Yang H, Rao Y, Miao J, Lu X. Intestinal Microbiota as an Alternative Therapeutic Target for Epilepsy. Canadian Journal of Infectious Diseases and Medical Microbiology. 2016; 1-6.
73. Şafak B, Altunan B, Topçu B, Eren Topkaya A. The gut microbiome in epilepsy. Microb Pathog. 2020 Feb;139:103853.
74. Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J Gastroenterol. 2017 Sep 7;23(33):6164-71.
75. He Z, Cui BT, Zhang T, Li P, Long CY, Ji GZ, Zhang FM. Fecal microbiota transplantation cured epilepsy in a case with Crohn's disease: The first report. World J Gastroenterol. 2017 May 21;23:3565-8
76. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? Stroke. 1996 Mar;27:550-8.
77. Chen R, Xu Y, Wu P, Zhou H, Lasanajak Y, Fang Y, et al. Transplantation of fecal microbiota rich in short-chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. Pharmacol Res. 2019 Oct;148:104403.
78. Wanchao S, Chen M, Zhiguo S, Futang X, Mengmeng S. Protective effect and mechanism of Lactobacillus on cerebral ischemia-reperfusion injury in rats. Braz J Med Biol Res. 2018;51:e7172.
79. Spychala MS, Venna VR, Jagodzinski M, Doran SJ, Durgan DJ, Ganesh BP, et al. Age-related changes in the gut

microbiota influence systemic inflammation and stroke outcome. Ann Neurol. 2018 Jul;84:23-36.
80. Singh V, Roth S, Llovera G, Sadler R, Garzetti D, Stecher B, et al. Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. J Neurosci. 2016 Jul 13;36:7428-40.
81. Zesiewicz TA, Sullivan KL. Treatment of ataxia and imbalance with varenicline (chantix): report of 2 patients with spinocerebellar ataxia (types 3 and 14). Clin Neuropharmacol. 2008 Nov-Dec;31:363-5.
82. Yu J, Fan Y, Wang L, Huang Y, Xia J, Ding L, et al. Intestinal Surgery Contributes to Acute Cerebellar Ataxia Through Gut Brain Axis. Front Neurol. 2019 Sep 20;10:995.
83. Ural K, Erdoğan H, Adak Hİ, Ateş DS, Kahraman D. Ataksik kedilerde fekal mikrobiyota transplantasyonu.Mehmet Akif Ersoy Üniversitesi Veterinerlik Fakültesi Dergisi. 2019; 4:34-6.
84. Du Y, Gao XR, Peng L, Ge JF. Crosstalk between the microbiota-gut-brain axis and depression. Heliyon. 2020 Jun 3;6:e04097.
85. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, et al. GABA-modulating bacteria of the human gut microbiota. Nat Microbiol. 2019 Mar;4:396-403.
86. Cai T, Shi X, Yuan LZ, Tang D, Wang F. Fecal microbiota transplantation in an elderly patient with mental depression. Int Psychogeriatr. 2019 Oct;31(10):1525-6.
87. Huang HL, Chen HT, Luo QL, Xu HM, He J, Li YQ, et al. Relief of irritable bowel syndrome by fecal microbiota transplantation is associated with changes in diversity and composition of the gut microbiota. J Dig Dis. 2019 Aug;20:401-8.
88. Umut S, Saryal S. Astım Tanı ve Tedavi Rehberi. Türk Toraks Dergisi. 2010;11:e1-e15.
89. Arrieta MC, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B. The intestinal microbiome in early life: health and disease. Front Immunol. 2014 Sep 5;5:427.
90. Kang Y, Cai Y. Future prospect of faecal microbiota transplantation as a potential therapy in asthma. Allergol Immunopathol (Madr). 2018 May-Jun;46:307-9.
91. Hunt JR, Martinelli R, Adams VC, Rook GA, Brunet LR. Intragastric administration of Mycobacterium vaccae inhibits severe pulmonary allergic inflammation in a mouse model. Clin Exp Allergy. 2005 May;35:685-90.
92. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, et al; CHILD Study Investigators, Mohn WW, Turvey SE, Finlay BB. Early infancy microbial and metabolic alterations affect the risk of childhood asthma. Sci Transl Med. 2015 Sep 30;7(307):307ra152.
93. Ekmekçi AM, Erbaş O. The role of intestinal flora in autism and nutritional approaches. Demiroğlu Bilim Üniversitesi Florence Nightingale Transplantasyon Dergisi. 2020;5:061-9.
94. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy--a Spanish prospective case-control 6-month follow-up study. Pediatr Allergy Immunol. 2010 Mar;21(2Pt 2):e394-400.
95. Topal E, Kashani S, Arda B, Erbaş O. Milk, and Cancer: Is There any Relation?. Journal of Experimental and Basic Medical Sciences. 2021;2:34-40.
96. Rask C, Evertsson S, Telemo E, Wold AE. A full flora, but not monocolonization by Escherichia coli or lactobacilli, supports tolerogenic processing of a fed antigen. Scand J Immunol. 2005 Jun;61:529-35.
97. Feehley T, Plunkett CH, Bao R, Choi Hong SM, Culleen E, Belda-Ferre P, et al. Healthy infants harbor intestinal bacteria that protect against food allergy. Nat Med. 2019 Mar;25:448-53.
98. Abdel-Gadir A, Stephen-Victor E, Gerber GK, Noval Rivas M, Wang S, Harb H, et al. Microbiota therapy acts via a regulatory T cell MyD88/RORγt pathway to suppress food allergy. Nat Med. 2019 Jul;25:1164-74.
99. Howley PM. Gordon Wilson Lecture: Infectious Disease Causes of Cancer: Opportunities for Prevention and Treatment. Trans Am Clin Climatol Assoc. 2015;126:117-32.
100. Duvallet C, Gibbons SM, Gurry T, Irizarry RA, Alm EJ. Meta-analysis of gut microbiome studies identifies disease-specific and shared responses. Nat Commun. 2017 Dec 5;8:1784.
101. Xu K, Jiang B. Analysis of Mucosa-Associated Microbiota in Colorectal Cancer. Med Sci Monit. 2017 Sep 14;23:4422-30.
102. Wu X, Zhang T, Chen X, Ji G, Zhang F. Microbiota transplantation: Targeting cancer treatment. Cancer Lett. 2019 Jun 28;452:144-51.
103. Ünal NG. Fekal Mikrobiyota Transplantasyonu. Güncel Gastroenteroloji. 2016;20: 437-41.