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

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. Fecal microbiota transplantation was first applied to 30 ulcerative colitis patients who were resistant to medical treatment by Uygun et al. 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.

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

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, Rotavirus, Adenovirus, Enterovirus, Parechovirus, Sapovirus, Norovirus, Astrovirus, 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.

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.

**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. 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. 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.

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.
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. 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%. 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. The application of FMT delivered via the nasoduodenal route was evaluated as superior to the standard oral vancomycin applied in the treatment of CDI. 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.

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. 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. 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. 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.

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. Dysbiosis is effective in heart diseases as well as in various diseases. In addition, intestinal-derived endotoxin trimethylamine N-oxide, which increases with the consumption of choline, L-carnitine, and phosphatidylcholine, has been associated with heart diseases such as atherosclerosis. 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. 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. 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. The basic mechanism of insulin resistance is considered to be a defect in insulin activity. The relationship of gut microbiota with insulin resistance is based on dysbiosis. Dysbiosis has been found with an increase in Clostridium cocoides and Atopobium cluster species in the intestines of individuals with type 2 diabetes. Pharmaceuticals that cause dysbiosis are also known to cause insulin resistance and glucose intolerance. 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. 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. Fecal microbiota transplantation was applied to 18 individuals with metabolic syndrome and a significant increase in insulin sensitivity was observed in nine individuals. 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.

**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. 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. While there was a 26% decrease in fecal Streptococcus species, a 5% increase was found in Bifidobacteria species. Amyloid and Tau protein pathology in the brain was reduced after FMT was administered to mice experiencing Alzheimer’s-like symptoms. An increase in cognition and a decrease in systemic inflammation have been reported with this change.

**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. It has been determined that Clostridial species are more common in the intestinal microbiota of children with autism. 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. 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. A decrease in symptom severity, social impairment, problem behaviors, and cerebral oxidative stress is observed in autism after FMT. 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.

**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. 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. 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. 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. 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. In the diagnosis of Parkinson’s disease, an increase in dopaminergic neurons and a decrease in motor symptoms are observed after FMT.

**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. 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%. 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. A significant decrease in Proteobacteria species and an increase in Bacteroidetes, Prevotella, and Bifidobacterium species were found with the ketogenic diet applied in the treatment of epilepsy. 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. 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.

**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. 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. 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. 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. 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. 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.

**ATAXIA AND FECAL MICROBIOTA TRANSPLANTATION**

Ataxia is known as a neurodegenerative disorder characterized by impaired walking, balancing, and speech activities that require coordination. 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. 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.
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.\[87\]

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.\[84, 95\] 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.\[98\]

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.\[92, 93\]

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.

Declaration of conflicting interests
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The authors received no financial support for the research and/or authorship of this article.

REFERENCES
19. Erbas O, Pala HG, Pala EE, Oltulu F, Aktug H, Yavasoglu


79. Spychala MS, Venna VR, Jagodziński M, Doran SJ, Durgan DJ, Ganesh BP, et al. Age-related changes in the gut


