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Review Article

Efficacy of Faecal Transplant Therapy in Non-alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is caused due to the tendency of the liver to build up fat in the liver causes Steatohepatitis. Unfortunately, in the present scenario, no specific treatment modality is available for a complete cure. The only way to manage this by lifestyle changes such as healthy diet, exercise, and weight management, but often difficult to guarantee for cure as well. Several human studies have legitimate evidence for the differences in the gut microbial population in patients with non-alcoholic steatohepatitis or non-alcoholic fatty liver disease. It is interesting to observe that even the characteristics of the gut microbiota between lean and obese patients varied in a wide range, and the patients in the two groups showed different responses to faecal transplant treatment. Faecal transplant therapy (FMT) could improve both lean and obese patients, but the treatment effect on lean patients was more promising than on obese patients. Taking advantage of FMT to prebiotic with beneficial bacteria could be a future challenge and success in therapeutics to cure non-alcoholic fatty liver disease.

Keywords: Non-alcoholic fatty liver; steatohepatitis; gut dysbiosis; rebiosis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease having a complex pathophysiology, yet to be well understood. This silent the disease has a tendency to build up fat in the liver which includes inflammation (NAFL) and with inflammation steatohepatitis (NASH). NASH resembles hepatitis caused by alcohol use, though it stems from something else. This disease is most often associated with being overweight, and having high blood lipids, and blood sugar. The global estimated prevalence of 25% in adults varies between countries, due to differences in age, gender, ethnicity, or dietary habits,including other reasons in patients who suffer from NAFLD. In addition to the accumulation of fat and liver damage, NAFLD is also responsible for obesity, metabolic syndrome, and type 2 diabetes [1]. NAFLD is a multi-systemic disease since it extends in the development of cirrhosis, or hepatocarcinoma, increased risk of cardiovascular disease, and extra hepatic cancer. Hepatic lipid accumulation from the absorption of circulating free fatty acids (FFAs), de novo lipogenesis, and dietary fats source leads to the development of NASH. Genetic factors, oxidative stress, mitochondrial dysfunction, pro-inflammatory factors, or gut-liver axis, and dysbiosis of the gut microbiome are also causative factors for NASH [2]. According to one estimate in 2030 non-alcoholic steatohepatitis (NASH) will increase by 15–56% [3].

Unfortunately, there is still no specific treatment available. Life style changes such as healthy diet, exercise, and weight loss, is the only therapeutic recommendation available right now, often difficult to guarantee as well [4-5].Considering the role of microbiota in the development and progression of NAFLD, alteration to intervene in the gut microbiota (GM) composition represents a possibility of promising treatment modality[2].

Possible relationship between microbiota and fatty liver diseases 100 trillion microorganisms (i.e., bacteria, viruses, parasites, and fungi) are estimated in the human gut, colonizing the gastrointestinal tract taking the responsibility of maintaining homeostasis. Specifically, 95% of these are *Firmicutes* (gram-positive), *Bacteroidetes* (gram-negative) and Actinobacteria (gram-positive) phyla. Disturbance of the balance between beneficial and pathogenic bacteria leads to a condition termed "dysbiosis" [6-7].

Several human studies have legitimate evidence for the differences in the gut microbial population in patients with non-alcoholic steatohepatitis

(NASH) or non-alcoholic fatty liver disease (NAFLD), compared with healthy controls. Barrio et al., [2] have tabulated the studies done to confirm that dysbiosis observed in patients with NAFLD and non-alcoholic NASH. Furthermore, apart from increased endotoxemia, people with NAFLD have increased intestinal permeability, that correlates with bacterial overgrowth in the small intestine and the severity of steatosis. In addition, patients with NALFD have increased lipopolysaccharide (LPS) -binding peptide levels in the plasma, even higher in liver and correlate to TNF-α mRNA expression in liver tissue, pointing toward a role for endotoxemia in inflammatory liver steatosis since TNFα is a powerful pro-inflammatory agent [8].

Disruption of the intestinal epithelial and gut vascular barrier is proven as an early and prerequisite events in the development of NASH related to dysbiotic microbiota [9;10]. Mouries et al. [11] also suggested that not only bacterial products but also the bacteria themselves will be able to reach the liver, since bacteria in the liver parenchyma of mice fed with a high-fat diet (HFD) was identified. Possibly bacteria and their metabolites can also reach the liver, through the portal system, and induce an inflammatory response, liver injury and fibrosis [11]. Bauer [12] could colonize germ-free mice with stool microbes from 2-week-old infants born to obese mothers (Inf-ObMB) and showed an increase in histological signs of periportal inflammation, intestinal permeability and accelerated NAFLD progression when exposed to a Western-style diet [12].

FMT and Non-alcoholic fatty liver disease

FMT-dependent rebiotic in non-alcoholic fatty liver diseases ascertaining the efficiency in modulating gut microbiota to bring the gut microenvironment back to a healthy state is of great focus in the present scenario to escape from the side effects of the drug as well as the non-availability of treatment modality for a complete cure. A fresh fibre fiber-rich diet provides growth substances to microbes but processed food leads to the impairment of the gut barrier and an alteration of gut microbiota (GM). A high-salt diet is closely associated with a reduction of *Lactobacillus abundance* [13]. Exercise has an impact on the GM composition since it has been witnessed that in obese and overweight individuals, energy restriction, and a Mediterranean diet with physical activity reduced *Firmicutes*, especially *Lachnospiraceae*, after one year of intervention [14]. FMT is a treatment intended to restore a patient's disturbed GM, by transferring minimally manipulated donor stool to the gut of the patient [2-15]. Limited studies indicated that microbiota-mediated effects on liver phenotype in mice model. In mice, antibiotics can reduce portal endotoxin levels and hepatic accumulation of lipids [16]. A human intervention trial, albeit not placebo-controlled, showed a decrease in intrahepatic triglyceride content measured by magnetic resonance spectroscopy upon the addition of probiotics to usual care [17].

Recently, however, the focus has been on the role of ethanoL-producing microbes in the etiology of NASH and NAFLD bridging between alcoholic and 'non- alcoholic' causes of steatohepatitis through the microbiome [18]. The use of antibiotics was suggested to have a long-term effect on the intestinal microbiota and its metabolites, at the expense of even affecting liver function through the "gut-liver" axis [19]. Antibiotic exposure may enhance the intestinal immune response and induce ROS accumulation and mitochondrial abnormalities in hepatocytes, thereby aggravating the adverse effects observed in HSD-fed mice [20].

Altering gut microbiota dysbiosis, by FMT was found effectively to improve the manifestations of NAFLD in animal models [5]. Therefore, human trials to apply FMT to treat patients with NAFLD in therapeutics has become an the attractive trend in the present situation similar to other nervous and non-nervous human diseases [21-30]. Xue, et al., [5] performed a randomized clinical trial to verify if the effects of faecal microbiota transfer from healthy donors can attenuate NAFLD and NASH severity. A total of 75 cases were recruited for the study, divided into the FMT group (n = 47), the non-FMT group (n = 28) and 10 healthy individuals as the control group. In the FMT group, 15 cases (31.9%) were lean and 32 cases (68.1%) were obese. Rebiosis with the help of FMT was able to decrease the fat accumulation in the liver in addition to significant differences in the clinical features of the disease and gut microbiota between lean and obese NAFLD patients. Moreover, FMT had better effects on gut microbiota reconstruction in lean NAFLD than in obese NAFLD patients [5]. Until now, only few human studies on the efficacy of FMT in the clinical treatment of NAFLD have been reported. The results of the randomized control trials have given a clue that FMT has the potential to reduce small intestinal permeability in patients with NAFLD [31]. Witjes et al. [32] also indicated that FMT from healthy donors could affect even hepatic gene expression and the plasma metabolites involved in inflammation and lipid metabolism suggesting the crosstalk between gut microbiota composition and NAFLD. Gut microbiota dysbiosis in patients with NAFLD was indicated by reducing bacterial diversity and decreasing beneficial bacteria resulting in metabolic disorders and opportunistic pathogen infection. Bacteroidetes, rumen bacteria, Christen senellaceae, and a few other bacteria were significantly reduced in patients with NAFLD. Bacteroidetes and rumen bacteria produce more butyric acid, which has the capability to protect the intestinal mucosal barrier [33] and enhance the body's resistance to metabolic disorders caused by a high-fat diet are reduced [34]. Both Bacteroidetes and Muribaculaceae belong to the Bacteroidetes family, of which the Prior FMT group (pri FMT group) had a significantly lower proportion than the post-FMT group (po-FMT group) or the healthy group. There was no significant difference in certain bacterial contents between the po-FMT and healthy groups. *Christensenellaceae* member of the *Firmicutes* family is widely prevalent in the intestines and mucous membranes of humans as well as animals. In terms of genus, 14 genera of bacteria were significantly reduced in the intestinal tract of NAFLD patients, most of which are probiotics related to the maintenance of normal metabolism, immunity, and intact mucosal barrier. Christensenellaceae, was found to be significantly lower in the pri-FMT group compared to the po-FMT and healthy groups. Compared to the healthy group, the pri-FMT group had less proportions of the following 14 types of bacteria: *Bacteroides, Christensenellaceae R 7, Metagenome, Ruminococcus 1, Tyzzerella 3, [Eubacterium] coprostanoligenes group, [Eubacterium] ruminantium group, Intestinimonas, Mitsuokella, Rikenellaceae RC9 gut group, Roseburia, and Subdoligranulum* .

On the other hand, Escherichia–Shigella were more abundant in the pri-FMT group, but less in the po-FMT group. Surprisingly Escherichia–Shigella an opportunistic pathogen is closely related to systemic inflammatory response and impaired intestinal barrier was significantly increased [5]. A recent meta-analysis, which included 15 studies published from 2012 to 2020, showed that NAFLD patients had a greater abundance of *SchEerichia, Prevotella* and Streptococcus and less of *Coprococcus, Faecalibacterium* and *Ruminococcus*, but the significant heterogeneity limited the drawing of conclusions [35]. Xue, et al.[5] suggested that the difference in the gut microbiota which may be

one of the main reasons for the differences between lean and obese NAFLD patients in their trial. The number of harmful bacteria involved in the pathogenesis of fatty liver and related to inflammatory reactions was increased more obviously in lean than in obese NAFLD patients, and the number of bacteria negatively correlated with body weight and blood glucose was also increased. It is suggested that the damage of the intestinal mucosal barrier in obese NAFLD patients can intensify the release of "harmful bacteria."

It is interesting to observe that the characteristics of the gut microbiota between lean and obese patients with NAFLD varied in a wide range, and the patients in the two groups showed different responses to FMT. At the phylum level, the abundance of *Actinobacteria* in lean NAFLD patients was significantly higher than that in obese NAFLD patients. At the order level, the abundance of *Desulfovibrionales* in lean NAFLD patients was significantly elevated than that in obese NAFLD patients. At the family level, the abundance of *Tannerellaceae* in lean NAFLD was increased compared to that in obese NAFLD patients. At the genus level, the abundance rates of *Prevotella 2, Lachnospiraceae nk4a136 group, Lachnospiraceae nd3007 group, [Eubacterium] Coprostanoligenes, Mitsuokella, and Fusicatenibacter* in lean NAFLD patients were significantly lower than those in obese NAFLD patients. At the species level, the abundances of Bacteroides copro cola DSM 17136 and uncultured Roseburia sp. in lean NAFLD were significantly higher than those in obese NAFLD patients, while *Bifidobacterium longum subsp. longum* was significantly higher in lean NAFLD than in obese NAFLD patients. *Actinobacteria, Desulfovibrionales, Bacteroidaceae, Bacteroides, and [Ruminococcus] gnavus group were* significantly decreased in the gut of lean NAFLD patients after FMT. On the other hand significant up regulation of *Selenomonadales, Veillonellaceae, Prevotella 2,[Eubacterium] coprostanoligenes group, [Eubacterium] ruminantium* group, human gut *metagenome*, and uncultured *Roseburia sp*. after FMT. Xue, L et al., [5] pointed out in this study that the proportions of *Prevotella 2,* [*Eubacterium] coprostanoligenes* group, and [*Eubacterium] ruminatum*

the group before treatment was all 0%, which then significantly increased after FMT, while the proportion of [Ruminococcus] gnavus group before FMT was 2.9%, which then decreased to 0% after FMT. Moreover, the proportion of *Bacteroidaceae* decreased from 40.6% to 35.7%, while that of *Bacteroide*s decreased from 51.5% to 38.1% after treatment. It is significant to observe, the proportions of Bacteroidaceae and Bacteroides in lean NAFLD patients before FMT were higher but decreased after FMT identifying athe significant result is that gut dysbacteriosis can be induced due to the imbalanced ratio of Bacteroidaceae to Bacteroides. In obese NAFLD patients, *Rikenella RC9* gut group and *Alistipes* were significantly decreased after FMT, while *Ruminococcus* 2 and Prevotella 2 were significantly upregulated. Moreover, *Lactobacillus* was slightly increased after FMT. In obese patients, NAFLD is mainly due to abnormal lipid deposition caused by excessive intake and obesity leading to further damage of the gut microbiota since significant improvement was noticed after interventions of diet control, weight loss, and exercise. On the other hand, in lean patients decreased number and diversity of beneficial gut microbiota, was more sensitive to the therapeutic effects of FMT which can be rectified by supplementing with gut microbiota. FMT could improve NAFLD in both lean and obese patients, but the treatment effect of FMT on lean patients was more promising that on obese patients.

Conclusion

FMT had beneficial effects on the improvement of lean than obese NAFLD patients. Lean and obese patients with NAFLD showed significant differences both in clinical manifestations and in the gut microbiota characteristics, mainly due to the different mechanisms of the gut microbiotadisorder. Prevalence of decreased gut microbiota numbers, butyrate-producing bacteria, and increased inflammation-inducing bacteria are responsible for the development of NAFLD. Taking advantage of FMT to rebiosis with beneficial bacteria could be a future challenge in therapeutics.

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