

INTEGRATING 'GUT-LIVER AXIS' PRINCIPLES WITH TRADITIONAL CHINESE MEDICINE COLON DIALYSIS FOR MAFLD MANAGEMENT

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Abstract: Metabolic associated fatty liver disease (MAFLD), a complex multi-system metabolic disorder, inflicts chronic harm upon the liver, progressing from hepatic steatosis to severe conditions such as non-alcoholic steatohepatitis, liver fibrosis, cirrhosis, and even hepatocellular carcinoma. This ailment, previously referred to as non-alcoholic fatty liver disease (NAFLD), is intricately linked to metabolic dysfunctions induced by factors such as obesity, type 2 diabetes, hypertension, dyslipidemia, and metabolic syndrome. In recognition of the substantial role of metabolic dysfunction, NAFLD was renamed MAFLD in 2020. MAFLD has emerged as a prevalent global chronic liver ailment, with its prevalence steadily increasing from 25% in 2016 to 32% in 2022. Presently, the U.S. Food and Drug Administration (FDA) has not approved any specific drugs for MAFLD treatment, underscoring the challenge posed by its heterogeneity and intricate pathology.

The primary focus of MAFLD treatment is centered on managing liver diseases, addressing metabolic syndrome, and mitigating complications. This approach aims to reduce liver fat accumulation, alleviate inflammatory damage induced by fat oxidation, and hinder the progression of hepatitis and liver fibrosis.

Keywords: Metabolic associated fatty liver disease (MAFLD), Non-alcoholic fatty liver disease (NAFLD), Liver fibrosis, Hepatic steatosis, metabolic dysfunctions.

1. Introduction

Metabolic associated fatty liver disease (MAFLD) is a multi-system metabolic disorder that causes chronic damage to the liver. It includes a range of diseases from the initial hepatic steatosis to the more severe non-alcoholic steatohepatitis, liver fibrosis, cirrhosis, hepatocellular carcinoma, etc [1], as shown in Figure 1. MAFLD was formerly known as nonalcoholic fatty liver disease (NAFLD). Studies have found that [2] metabolic dysfunction caused by obesity, type 2 diabetes, hypertension, dyslipidemia and metabolic syndrome is closely related to the complex mechanism of NAFLD development. So, in order to no longer rule out a diagnosis of heavy alcohol consumption or other chronic liver diseases, while placing more emphasis on the role of metabolic dysfunction in it, experts renamed NAFLD MAFLD in 2020 [3]. MAFLD is now a common chronic liver disease in the world, and the prevalence of MAFLD has been on the rise in recent years, with the global prevalence increasing from 25% in 2016 to 32% in 2022 [4]. Due to the

heterogeneity of this patient population and the complexity of the pathology, there are currently no specific drugs approved by the U. S. Food and Drug Administration (FDA) for the treatment of MAFLD [5]. The treatment of MAFLD is mainly for liver diseases and related metabolic syndrome and

complications, by reducing liver fat accumulation, alleviating the inflammatory damage caused by fat oxidation to the liver, and preventing the process of hepatitis and liver fibrosis.

Traditional Chinese medicine (TCM) is the precious wealth accumulated by the Chinese nation in the process of long-term struggle against diseases. In recent years, the clinical research on TCM colon dialysis has shown great advantages in the treatment of various diseases, but there are few researches in the field of liver disease. The incidence of MAFLD is increasing year by year, and prevention and treatment are urgent. Colon dialysis is a continuously developed and improved treatment method based on the theory of "gut-liver axis" and the traditional retention enema. The use of traditional Chinese medicine colon dialysis for the treatment of MAFLD has the advantages of simple, convenient, inexpensive and testing, and can provide safe and effective traditional Chinese medicine treatment for the diagnosis and treatment of MAFLD. Based on the theory of "gut-liver axis", this paper expounds the treatment of MAFLD with traditional Chinese medicine colon dialysis, in order to provide a new reference for the clinical treatment strategy of MAFLD.

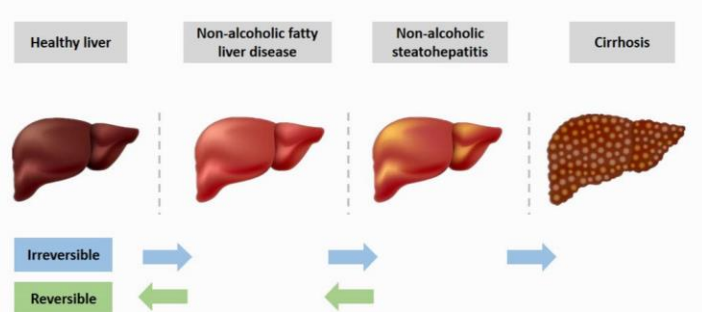


Figure 1: The developing phases of MAFLD

2. Gut-liver axis

Pathophysiological Marshall first proposed the "gut-liver axis" theory in 1998, describing the two-way communication process between the intestine and the liver through the portal vein system, biliary tract and systemic circulation [6]. From the perspective of modern medicine, the anatomical position relationship and physiological and pathological relationship between liver and intestine were analyzed. Intestine and liver have the same embryological origin -- the foreintestine, and both participate in the immunity of the body and maintain the homeostasis of the body [7]. The gut-liver axis is a two-way interaction between the gut and its microbes and the liver, which is influenced by diet, genetics, and environment, and is realized through bile duct, portal vein, and systemic circulation. On the one hand, the liver transports synthesized bile acids and immunoglobulin A (IgA) and other bioactive mediators to the intestinal lumen through the bile duct. On the other hand, body microbial metabolites such as secondary bile acids in the gut and pathogen-associated molecular patterns (PAMPs) can be transported to the liver via the portal vein and regulate liver function. In addition, free fatty acids, choline metabolites and ethanol metabolites in the gut can be transported to the liver through systemic circulation [8]. The hepatointestinal circulation of bile acids is a key factor in the interaction between the gut and the liver [9]. Bile acids are coupled by farnesoid X receptor (FXR) and G protein-coupled bile acid receptor1 (Gpbar1) regulate metabolic pathways and inflammatory responses in the body, among which FXR is a core pathway that regulates lipid and glucose metabolism and is involved in maintaining intestinal homeostasis [10]. Intestinal flora interacts bidirectional with bile acids. Bile acids affect the composition of intestinal flora by shaping intestinal immunity and part of endogenous antibacterial properties. Intestinal flora can metabolize bile acids into secondary bile acids, so changes in the composition of intestinal flora will break the balance between primary bile acids and secondary bile acids in the body, thus promoting the progression of liver diseases [11]. Under normal circumstances, the intestinal barrier can effectively prevent intestinal microorganisms and harmful substances produced by their metabolism from entering the liver. When the intestinal barrier is damaged, harmful

substances in the intestine will invade the liver and participate in the occurrence and development of liver diseases [12]. The disturbance of the gut-liver axis plays an important role in the development of liver disease. In MAFLD, the high fat diet (HFD) leads to an increase in secondary bile acids, PAMPs, ethanol and their metabolites in the gut and a decrease in SCFAs by inducing changes in the composition of the gut microbes. Upregulation of secondary bile acids inhibits the FXR signaling pathway in the gut, resulting in decreased antimicrobial peptide synthesis, intestinal barrier disturbance, and increased primary bile acid synthesis in the liver [13]. The increase of ethanol in the intestine and the decrease of SCFAs promote the decrease of antimicrobial peptide synthesis, the disturbance of the intestinal epithelial barrier, and thus the increase of intestinal permeability and the increase of PAMPs into the liver through the portal vein. On the one hand, the increase of PAMPs causes intestinal inflammation by activating intestinal immune cells and promoting the release of inflammatory cytokines, which further destroys the intestinal epithelial barrier. On the other hand, it leads to liver inflammation and promotes the progression of liver diseases [14].

As an important component of intestinal mucosal barrier, intestinal flora plays an important role in maintaining intestinal homeostasis and intestinal health. In the intestinal tract of healthy adults, anaerobic bacteria such as bifidobacterium and bacterioid bacteria are absolutely dominant [15]. Probiotics and pathogenic bacteria are interdependent, interact and restrict each other to keep the liver reticuloendothelial system in an activated state and prevent harmful substances in the intestine from entering the liver through the portal vein. When high-fat diet, increased pressure, stress, infection and other factors cause the imbalance of the internal environment of the body, intestinal flora disorders, changes in the number, type and survival site of bacteria, loss of intestinal mucosal barrier function, increased permeability, and displacement of a large number of bacteria and endotoxins, which enter the liver through the gut-liver axis, causing chronic inflammation and damage of the liver. It may even cause functional damage of multiple organs in the whole body. However, the decline of liver function will affect the synthesis of bile acids, weaken the effect of inhibiting intestinal harmful bacteria and clearing endotoxin, and easily lead to endotoxemia, forming a vicious cycle.

3. Traditional Chinese medicine

TCM classifies MAFLD as "accumulation", "hypochondriac pain", "liver fullness", "fat qi" and other categories. The concept of "liver" in Chinese medicine includes "liver" in Western medicine, and the function of "spleen" in Chinese medicine includes the function of "intestine" in Western medicine, and the digestion and absorption function of large and small intestine should belong to the functional category of spleen governing and transporting in Chinese medicine. In the anatomical position of traditional Chinese medicine, the liver is located in the right flank, while the large intestine is located in the abdominal cavity, and its upper mouth is connected to the small intestine at the stop door, and the lower end is immediately connected to the anus (soul door). Doctor Tang Zonghai was inspired by the anatomical knowledge of blood omentum in the Zang-fu organs of Western medicine, pointed out that "the diaphragm in the liver, the blood room, the bladder in front, the large intestine in back, Jueyin liver pulse, and the anus around the outside", the liver and the large intestine both blood around the intersection, the function of the Qi and blood, and the relationship with the soul door, jointly maintain the coordination of human zang-fu function. Traditional Chinese medicine believes that "liver is wood, wood qi chong and regulation, do not suppress depression, then the blood is smooth", "soil wood and reach", liver Qi on the large intestine in the movement of qi, especially the decline of turban qi, drops conduction of the final stage is fully reflected, liver drainage, then the human qi hub - spleen and stomach rise and fall turban, diet transport function is normal, So that the water grain is fine to the heart and lung, and promote the decomposed food to the small intestine, the dross to the large intestine. Chen [16] integrated traditional Chinese medicine theories with modern medical theories and proposed that "the liver is deposited in the large intestine", and believed that the liver uses the large intestine to reduce qi and expelling turbidification. Smooth opening and closing of the large intestine to expelling

turbidification will contribute to the normal physiological function of the liver, and the normal drainage of the liver will ensure the smooth drainage of the large intestine.

The generation and movement of qi and blood and the rise and fall of qi depend on the liver and spleen. The occurrence of MAFLD is mostly caused by emotional disorders or dietary disorders, the loss of spleen health and the obstruction of phlegm and blood stasis in the liver, so the treatment of MAFLD is mostly based on the method of soothing the liver and strengthening the spleen, removing blood stasis and turbidizing. Zhang ^[17] took the "gut-liver axis" as the theoretical core, and stimulated the intestinal epithelial cytoskeleton by massaging the abdomen, causing the remodeling of the skeleton structure and reassembling the apical junction complex, thereby reducing the permeability of the intestinal barrier, inhibiting lipopolysaccharide invasion of the liver and inhibiting the occurrence and development of MAFLD. Wang ^[18] found in the experiment that the liver-gallbladder soothing drugs in Da Chaihu decoction can significantly regulate the liver immune function and liver lipid metabolism, and the spleen-strengthening and phlegm-eliminating drugs can significantly improve the intestinal mucosal barrier function, which can simultaneously treat the "liver axis" and "intestinal axis", and has a good therapeutic effect on MAFLD model rats. Gao ^[19] self-prepared Yiqi Shugan Jianpi Decoction in the treatment of MAFLD patients showed significant improvement in clinical symptoms, liver function indexes, blood lipid indexes, etc. , indicating better clinical effect on liver and spleen homology in MAFLD patients. Wu ^[20] found in the experimental study that Yinchenlinggui could regulate the lipid metabolism of MAFLD rats, reduce liver inflammation, repair intestinal mucosal barrier, and achieve the purpose of treating MAFLD by regulating the gut-liver axis.

4. Traditional Chinese medicine colon dialysis

4.1. Brief introduction to colon dialysis

Traditional Chinese medicine colon dialysis treatment of MAFLD is a continuous development and improvement on the basis of traditional Chinese medicine retention enema. Colon dialysis is to clean the intestine by injecting filtered water into the human colon to remove the long-term accumulation of intestinal stool and intestinal endotoxin. The contact surface between the colonic mucosa and the colonic liquid is reperfusion, and the contact surface between the colonic mucosa and the colonic liquid is appropriately increased. The drug liquid absorbs various harmful toxins through the colonic mucosa and is discharged from the body to achieve the effects of lipid lowering, turbidity expelling and intestinal cleansing, adjust the imbalance of intestinal flora, and form a clean and effective colon environment. Then, according to the characteristics of the patient's disease, appropriate Chinese medicine was injected into the deep intestine, and the effective components of Chinese medicine were absorbed by the mucosa of the large colon to achieve the therapeutic effect. As shown in Figure 2, it is combined with intestinal cleansing, colon dialysis and colon administration in sequence, and has good clinical efficacy.



Figure 2: Traditional Chinese medicine colon dialysis procedure

4.2. Traditional retention enema vs. colon dialysis

With the traditional retention enema, the depth of the anal canal intubation is shallow, reaching as far as the far part of the colon, and the preservation time and quality of the drug liquid in the intestine are obviously limited. After enema, the patient's bowel intention is enhanced, and the frequency and effect of defecation are unstable.

Colon dialysis is a colon dialysis machine to inject dialysate and drugs into the intestinal cavity, with the help of computer control can realize the automatic perfusion and excretion of colon dialysate, and its temperature, flow, pressure automatic control and monitoring, to achieve a more intelligent

operation, improve the convenience of operation, safety and reliability. Thoroughly clean intestinal feces and toxins in the intestine on the high colon to adapt to human temperature. The perfusion tube has little stimulation to the anus, and the retention time and amount are balanced, and the effect is stable.

4.3. Traditional Chinese medicine colon dialysis treatment

According to the relevant literature, colon dialysis therapy has been widely used in the early and middle stages of chronic renal failure. For example, Zhang ^[21] used rhubarb colon dialysis to treat early and middle chronic renal failure, and the results showed that clinical symptoms were relieved, and all laboratory indicators (SCr, BUN, UA and MM) were reduced by more than 1/2 compared with those before treatment. Wei ^[22] divided patients with early and middle stage chronic renal failure into a treatment group (traditional Chinese medicine colon dialysis therapy) and a control group (traditional Chinese medicine enema based on syndrome differentiation). Experiments showed that the treatment group (effective rate of more than 90%) was superior to the control group in terms of both symptoms and biochemical indexes. In recent years, colon dialysis therapy has also been gradually applied to the field of liver disease. For example, Shi ^[23] selected 60 patients with chronic severe hepatitis who met the inclusion criteria, and conducted clinical observation with colon dialysis as the treatment group and routine and symptomatic supportive treatment as the control group. The treatment group (total effective rate of about 77%) was significantly better than the control group (total effective rate of about 23%). Wang ^[24] treated MAFLD with traditional Chinese medicine colon dialysis, the control group was treated with Western medicine, and the treatment group was combined with traditional Chinese medicine colon dialysis on the basis of Western medicine, with 73 cases in each group. The clinical efficacy, B-ultrasound, liver function and blood lipid of the treatment group were better than those of the control group.

4.4. Influence of traditional Chinese medicine colon dialysis on MAFLD

Clinically, many MAFLD patients often have excessive intestinal gas production such as constipation, bloating or diarrhea. Zhang ^[25] found that TCM enema could effectively relieve patients' clinical symptoms and signs, reduce liver function and lipid indexes, improve intestinal flora, and effectively prevent and treat MAFLD. Yuan ^[26] found in the clinical trials of patients with MAFLD that after colon dialysis treatment with traditional Chinese medicine, the patients' symptoms improved, their weight decreased, liver function and blood lipid improved, and blood uric acid decreased. Traditional Chinese medicine enema treatment, due to the shallow position, leads to insufficient absorption of drugs, and traditional Chinese medicine colon dialysis is the combination of colon dialysis therapy machine and traditional Chinese medicine lavage, is a new method to treat MAFLD. It makes full use of the colon's scavenging and absorption function, eliminates pathogens and toxins produced on the intestinal cavity and intestinal mucosa, and metabolic residual products in the body, and finally infuses special Chinese medicine preparations in the colon to absorb the effective components of drugs using the colon mucosa, thus playing a therapeutic role. Combined with relevant studies at home and abroad, it is found that intestinal flora disturbance and activation of immune-related factors play important biological functions in various pathological and physiological processes such as MAFLD. Traditional Chinese medicine colon dialysis treatment makes the active ingredients of traditional Chinese medicine directly contact with the colon mucosa to play a drug role, promote the timely excretion of toxins in the body, reduce gastrointestinal irritation, and significantly improve the clinical effect.

5. Summary and prospect

In recent years, MAFLD has become the most common chronic liver disease in the world, and the global prevalence continues to rise, which is one of the serious public health problems ^[27]. TCM is the precious wealth accumulated by the Chinese nation in the long-term struggle against diseases. In-depth study and scientific summary of the research progress of traditional Chinese medicine in the treatment of MAFLD will have an important influence and positive significance for the world medical development and life science research. Based on the theory of "gut-liver axis", this paper briefly expounds the

treatment of MAFLD by traditional Chinese medicine colon dialysis, hoping to provide new ideas and references for the clinical treatment of MAFLD. However, it is also found that the following problems need to be improved in the study of traditional Chinese medicine colon dialysis in the treatment of MAFLD. First of all, the active components of traditional Chinese medicine are complex, and multiple signaling pathways are involved between the multi-target action and the final biological effect. However, most studies on traditional Chinese medicine for MAFLD treatment focus on a single specific binding protein in one signaling pathway, while there is a lack of studies on the influence of other signaling functional active proteins and the functional integrity of other signaling pathways. Therefore, the synergistic effect of TCM colon dialysis on different signaling pathways can be further explored in combination with relevant drug-disease target prediction methods and gene editing methods, so as to better elucidate new functional molecules and network relationships in TCM colon dialysis treatment of MAFLD. Secondly, in order to further clarify the efficacy of the active ingredients of traditional Chinese medicine, the scale of clinical trials will be gradually increased, and large samples and multi-center randomized controlled studies will be paid attention to, in order to clarify the therapeutic effects of traditional Chinese medicine active ingredients on clinical patients with MAFLD and lay a foundation for future clinical drug promotion. Finally, traditional Chinese medicine colon dialysis has potential advantages in reducing the incidence of MAFLD complications, severe and critical diseases, and reducing mortality, and further evidence-based studies are needed to provide evidence.

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