

Discussion on the Relationship between Intestinal Flora Dysbiosis and Metabolic Fatty Liver Disease based on the Theory of "Spleen is the Guard"

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Abstract: "Spleen is the guard" means that the spleen has the function of resisting external evils and warming the body. "The spleen loses its guard". When the spleen is weak, phlegm, turbidity and blood stasis will invade the body and develop into metabolism-associated fatty liver disease (MAFLD). Dysregulation of intestinal flora can lead to the occurrence and development of MAFLD, so we can treat MAFLD by regulating intestinal flora as the target.

Keywords: Metabolism-associated fatty liver disease, Spleen is the guard, Intestinal flora dysbiosis.

1. Introduction

Metabolism-associated fatty liver disease (MAFLD), previously named non-alcoholic fatty liver disease (NAFLD), is a metabolic stress disorder closely related to insulin resistance and genetic susceptibility to fatty liver injury [1], with a complex pathogenesis and lack of effective drug therapy. MAFLD is the most common chronic liver disease worldwide, and a major cause of morbidity and mortality from related liver diseases [2]. Epidemiology shows that the overall prevalence of MAFLD in China has been higher than 29% [3], and the total global prevalence reaches 32.4% [2], and the prevalence is increasing year by year.

Gut microbiota (GM) is a general term for a variety of microorganisms designated to be planted in the gastrointestinal tract, which plays an important role in many aspects of the body, such as digestion, absorption, metabolism and immunity [4]. In recent years, it has been found [5] that intestinal flora dysbiosis is closely related to the pathogenesis of MAFLD. Therefore, regulating intestinal flora has become an emerging strategy for the treatment of MAFLD. In Chinese medicine, the theory of "spleen is the guard" has a similar function with intestinal flora. Therefore, based on the theory of "spleen is the guard", this paper elaborates on the dysregulation of intestinal flora and the occurrence of MAFLD, so as to guide the clinical treatment or drug research.

2. The Theory of "Spleen is the Guard" and GM

2.1 Connotation of the Theory of "Spleen is the Guard"

The theory of "spleen is the guard" was first published in Huangdi's Neijing, and it is written in the Ling Shu - Five Retaining Liquids and Fluids, "The five viscera and six bowels are dominated by the heart, the ears are listening to them, the eyes are waiting for them, the lungs are the phase, the liver is the command, the spleen is the guard, and the

kidney is the master," pointing out that each of the five viscera has its own function. "Wei" should have two meanings, one is "defending", and "Wei" is defined as the meaning of guarding in Shuo Wen Jie Zi. Lingshu says that "the spleen is the guardian, making it welcome food, and knowing good or bad by looking at the likes and dislikes of the lips and tongues", which is based on "the lips are the weather outside the spleen", which means that the health status of the spleen can be inferred by observing the changes of the lips, and the functions of the spleen in defending the body, resisting evil and preventing diseases can be highlighted. There is a saying in Leijing Zangxiang: "The spleen master transportation of water and grain to long muscles, the five viscera and six bowels are dependent on its nutrition, so the spleen is the main guard. Wei, the organs of the guard also. "Spleen as the source of the latter day, through the transportation of water and grain essence to nourish the five viscera and bowels, limbs and bones, guarding the internal organs. The second refers to the "Wei Qi", "Su Wen - paralysis theory" cloud: "Wei, the water and grain of the humongous gas. Its gas is very fast and slippery, and it cannot enter the veins. Therefore, through the skin, between the flesh, smoked in the membrane, scattered in the chest and abdomen", Wei Qi from the spleen and stomach produced by the essence of the water and grains, traveling outside the veins, not subject to the constraints of the vein, outside the skin, internal and internal organs, dispersed throughout the body. In the book "Medical Essentials - Zongqi, Yingqi and Weiqi", it is said that "Wei Qi, guarding the body... does not make foreign evil invasion," referring to the Wei Qi is full of the body is not easy to incur foreign evil. The Spiritual Pivot - Ben Zang says "Wei Qi, so the warmth of the flesh, full of skin, fat coupling, open and close the Secretary", emphasizing that the Wei Qi has the function of warming the internal and external, nourishing the coupling, open and close the pores of the sweat and so on. In summary, "spleen is the guard" means that the Spleen can guard the body from the internal and external aspects to maintain the normal operation of body functions.

2.2 Relationship between "Spleen is the Guard" and Intestinal Flora

The "spleen" in Chinese medicine has rich connotations and many functions. Anatomically, it corresponds to the spleen, stomach, duodenum, large and small intestines, pancreas, etc. in modern medicine; functionally, it covers digestive, immune, endocrine, blood and other systems [6]. The intestinal flora is very similar to the function of "spleen is the guard" in Chinese medicine. The theory of "spleen is the guard" is a generalization of the theory of "Spleen is the foundation of the later life", including the connotation that Spleen is the master of transportation and digestion [7]. Intestinal flora can ferment and degrade food, and in the process of fermentation and degradation, metabolites such as short chain fatty acids (SCFAs) will be produced, and SCFAs can provide energy for the metabolism of intestinal tissues, but the human body itself cannot produce this substance, and can only obtain it through external intake or metabolism of commensal bacteria, which is consistent with the theory of "the spleen is the master of transportation and transformation", i.e., the spleen can transport and transform water and grains into essence and nourish the body [8]. The spleen's ability to resist evil is similar to the immune regulation of the body by intestinal flora. The spleen and stomach can generate Wei Qi, and when Wei Qi is abundant, the body is less likely to incur external evils. Intestinal flora and mucosal immunity, immune cells, immunoglobulin, etc. are closely related, and together they form a peripheral barrier for the defense of the human body. The intestinal flora, which constitutes the biological barrier of the body, can participate in the body's immune defense, which can not only resist pathogenic bacteria, but also stimulate the development and maturation of the body's immune organs and maintain the balance of the body's immune system.

3. MAFLD and Intestinal Flora Dysbiosis

Intestinal flora is categorized into commensal, pathogenic and conditionally pathogenic bacteria. When the homeostasis of intestinal flora is disrupted, conditionally pathogenic bacteria and pathogenic bacteria are more likely to invade and colonize the body and cause disease. The body's first stop for receiving signals from the intestinal lumen is the liver, and the portal vein is the main route for blood returning from the gastrointestinal tract. Bioactive metabolites produced in the gut can travel from the intestinal lumen to the liver parenchyma through the portal vein as a fast track, which is known as the enterohepatic axis. Zhang Zhisu et al [9] showed that the level of beneficial bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Anaplasma* spp. in NAFLD group was lower than that of healthy control group, and pathogenic bacteria such as *Enterobacter* spp. and *Enterococcus* spp. were higher than that of healthy control group. Zhao Xiangyun et al [10] found that *Lactobacillus rhamnosus* intervention could significantly change the structure of intestinal flora induced by high-fat diet in mice, improve the diversity of intestinal flora, increase the abundance of beneficial bacteria such as *Lactobacillus* spp. and decrease the proportion of potentially pathogenic bacteria such as *Bacteroides anthropophilus* spp. and treat MAFLD by inhibiting inflammatory response and slowing down the fibrotic process. Under normal conditions, homeostatic equilibrium can be reached between flora and between flora and host, and pathogenic bacteria and their metabolites do not reach the liver through the intestinal

mucosal barrier [11]. When the composition or ratio of intestinal flora is imbalanced, the intestinal mucosa is damaged, the intestinal epithelial permeability is increased, and pathogenic bacteria and endotoxins pass through the enterohepatic axis exposing the liver to enterogenous bacterial products, they exacerbate the inflammatory process and the accumulation of fat, which affects the body's energy metabolism and contributes to the development of MAFLD [12]. Certain microbiota synthesize a variety of metabolites in the gut, such as SCFA, bile acids, choline, lipopolysaccharides, endogenous ethanol, etc., which can interact with the host, activate inflammatory responses, and promote the development of MAFLD [13,14]. SCFA intervenes in the development of MAFLD mainly by regulating glucose and lipid metabolism, repairing the intestinal barrier, ameliorating oxidative stress and influencing related signaling pathways [6]. Bile acids can promote the production of glucagon-like peptide-1 (GLP-1) by binding to its related receptors, thereby improving intestinal inflammatory response, reducing insulin resistance, and promoting lipid and bile acid metabolism [15]. Therefore, MAFLD can be improved by correcting the abnormalities of SCFA, bile acids and other metabolites.

4. Spleen Loss of Guard

In Chinese medicine, there is no name for MAFLD, and according to its characteristics, modern medicine categorizes it as "liver fetish", with spleen deficiency as the key to its pathogenesis [1]. Spleen is the foundation of the later day, which can transport and transform water and grain essence, and generate qi and blood. MAFLD can occur when the spleen and stomach are damaged by long-term dietary irregularities, or when the spleen is affected by emotional disorders, or when the spleen is weakened by liver depression, or when the spleen and stomach are weakened by prolonged illness. Zhang Zhongjing in the "Jin Gui Yao Liao - organs and meridians successive disease" proposed: "the treatment of the disease, see the liver disease, know that the liver transmission of the spleen, when the first solid spleen, four seasons of the spleen is not evil". The Spiritual Pivot - The Upper Diaphragm states, "When Wei Qi does not camp, evil Qi resides there." If the spleen is strong, the Wei Qi will be abundant, and it will not be easy for external evils to invade internally. If the "spleen loss of guard", spleen qi deficiency, transport and transformation of powerlessness, resulting in deficiencies in the Wei Qi, Wei external not solid, viscera loss of nourishment, the evil invasion. Long-term high-sugar and high-fat diet will increase the wind of harmful bacteria in the body, resulting in fat, sugar, protein and other nutrients can not be properly decomposed, water and grain essence micro-accumulation in the body, transport and transformation of the dereliction of duty, become turbid evil. Over time, this can lead to blood glucose, dyslipidemia and obesity, which will increase the burden on the spleen and stomach and become a potential risk factor for the development of MAFLD. The key to the development of diseases lies in the struggle between good and evil, the body's immune ability to decline, the lack of positive qi, then the evil to stay. Therefore, when the spleen is deficient, it is more susceptible to phlegm-dampness and damp-heat evils, and thus develops into MAFLD.

5. Clinical Application

MAFLD is currently treated by Western medicine mainly by improving poor lifestyle and treating the primary disease, and there is no specific drug. Chinese medicines contain rich chemical components, which have certain advantages in adjusting the structure of intestinal flora, and their active ingredients can regulate the functional structure and abundance of intestinal flora to maintain the balance of intestinal flora [16]. Based on the characteristics of multiple pathways and perspectives, TCM is effective in improving spleen deficiency and combating MAFLD.

5.1 Traditional Chinese Medicine Compound Treatment of MAFLD

Xiaoyao powder has the effect of harmonizing liver and spleen, relieving liver and relieving depression, nourishing blood and spleen. Jia Chen et al [17] found that it can increase beneficial bacteria and inhibit pathogenic bacteria, inhibit inflammation and reduce MAFLD liver injury and improve liver function by promoting the repair of intestinal mucosal barrier. Zhou Fang et al [18] found that Liver-sparing and Turbidity-reducing Drink could significantly improve the severity and TCM evidence points of MAFLD patients, and enterococci and *Escherichia coli* were significantly reduced, and *Lactobacillus* and *Bifidobacterium* were significantly increased in the treatment group. The Liver-Sparing and Turbid-Resolving Drink is made from the combination of Xiao Chaihu Tang and Si Reverse San, which has the function of liver-sparing, qi regulating, spleen-strengthening and turbid-resolving, and it can improve MAFLD by regulating the intestinal flora. Ling Gui Zhu Gan Tang has the function of warming yang and resolving drinking, strengthening the spleen and inducing dampness, which can improve MAFLD by warming and replenishing the damaged spleen yang. Studies have shown [19] that intermittent fasting combined with Ling-gui-zhu-gan Tang and probiotics can correct the intestinal flora disorder, restore the diversity of flora, and increase the richness and homogeneity of the flora of mice with MAFLD. When Yinchenhao Powder was used for the treatment of MAFLD patients, the levels of *Escherichia* and *Enterococcus* were significantly lower after treatment than before treatment, and the levels of *Bifidobacterium* and *Lactobacillus* were significantly higher than before treatment. Yinchenhao Powder has the effects of resolving phlegm and subduing turbidity, clearing the heart and tranquilizing the mind, expelling phlegm and inducing dampness, strengthening the spleen and benefiting the qi, and it can effectively regulate the level of intestinal flora and inhibit the oxidative stress response and inflammatory factor activity [20]. With the efficacy of warming the middle yang and tonifying spleen qi, Fuzi Lizhong decoction can regulate the intestinal flora and its metabolites, modulate downstream cytokines by acting on the expression of key proteins of the relevant signaling pathways on the intestinal-hepatic axis, and thus improve MAFLD [21].

5.2 Traditional Chinese Medicine Monomer Treatment of MAFLD

Exocarpium Citri Rubrum is good at regulating qi and resolving phlegm, so that endogenous phlegm-dampness can

be transported and transformed, liver qi can be regulated and spleen qi can be transported, and MAFLD can be cured. Treatment with tangerine red extract limonene plus dietary control can somewhat improve the distribution of intestinal flora in phlegmatic patients with MAFLD, resulting in an increase in the relative abundance of beneficial bacteria (intestinal *Catenibacteriu*, *Lactobacillus* spp., and other genera) and a decrease in the relative abundance of harmful genera (*Clostridium stenotrophicum* spp. 1, etc.) [22]. *Schisandra chinensis* aqueous can normalize the diversity of intestinal flora in mice, making the abundance of beneficial genera such as *Mycobacterium anisopliae*, *Mycobacterium thickum*, *Mycobacterium wartyi*, norank_f_Muribaculaceae, *Streptococcus* spp. and *Akkermansia* obviously tend to be higher than that of healthy mice, and it can exert a therapeutic effect on MAFLD by correcting the disturbance of the intestinal flora of mice with NAFLD [23]. Quercetin is a naturally occurring flavonoid that is metabolized primarily in the intestinal tract, where it is converted by gut microbes and then absorbed by the body. Quercetin alters the abundance of beneficial bacteria in the mouse intestine, such as *Micrococcaceae*, *Micrococaceae*, and *Ackermannia* spp. It can reduce plasma lipopolysaccharide and ethanol levels, and restore the production of short-chain fatty acids and the integrity of the intestinal barrier by regulating the balance of the intestinal flora [24].

6. Summary and Prospect

The theory of "spleen is the guard" is a generalization of the theory that the Spleen is the basis of the later day, which includes the connotation that the Spleen is the master of transportation, etc. It is highly consistent with the function that the intestinal flora plays in the human body. Herbal compounds and herbal monomers can improve the intestinal microecology by improving the intestinal flora and its related products for the treatment of MAFLD. The mechanism of action regarding intestinal flora has been relatively well studied in MAFLD, and the effectiveness of TCM in improving intestinal flora in treating related diseases has also been demonstrated. In the future, the treatment of MAFLD in TCM should be based on a holistic view, with "spleen is the guard" as the focus, and the treatment should be based on the theory of spleen, so as to give full play to the unique advantages of TCM in regulating the intestinal flora for the treatment of MAFLD.

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