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Exploring Acupuncture for Non-Alcoholic Fatty Liver Based on Insulin Resistance

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Abstract: *Taking insulin resistance (IR) as the entry point, based on the effect of IR on the pathogenesis of NAFLD, we investigated the mechanism of acupuncture to modulate IR in the treatment of NAFLD, and proposed the combination of Yu points and the effect of electroacupuncture stimulation parameters on the efficacy of acupuncture, in order to provide directions for later research and clinical practice.*

Keywords: *Insulin resistance; Acupuncture; Non-alcoholic fatty liver disease*

1. Introduction

Currently, nonalcoholic fatty liver disease (NAFLD) is a major factor in the development of chronic liver disease worldwide, with approximately one-third of the population in developed countries worldwide suffering from NAFLD [1], and as the disease progresses to nonalcoholic steatohepatitis (NASH), its complications at the end stage are a major indication for liver transplantation [2]. Because NAFLD is often accompanied by metabolic dysfunction, it is now accepted to change the definition of NAFLD to metabolic-related steatohepatitis [3,4], which is a major cause of cardiovascular, gastrointestinal, oncological, and neurodegenerative pathologies. If steatosis is compared to a "pedal", a series of factors that aggravate it, i.e., inflammation, are like a "foot" on the "gas" [1,5]. In addition, NAFLD, as a metabolic disease, is often characterized by primary obesity and IR, which has been experimentally proven to be a key pathogenic factor in promoting hepatocellular steatosis [6]. This review provides an overview of recent studies related to IR and NAFLD pathogenesis and possible mechanisms of action, and discusses the effect of acupuncture in regulating IR to treat NAFLD, which can help further clinical understanding and treatment.

2. IR and NAFLD

NAFLD is the hepatic manifestation of the metabolic syndrome, and IR refers to the decreased efficiency of insulin uptake and utilization of glucose, which is the central pathological manifestation of the metabolic syndrome. "The presence of IR is known as the first strike, accompanied by an increase in free fatty acids (FFA) and subsequent steatosis of hepatocytes, with the result that hepatocytes are more vulnerable to the second strike. After the initial blow, hepatocytes further experience oxidative stress and lipid peroxidation, increased intracellular production of reactive oxygen species (ROS) and tumor necrosis factor alpha (TNF-α), decreased ATP synthesis, and increased oxygen radicals, leading to activation of inflammatory factors, manifested as apoptosis and necrosis of hepatocytes, and the generation of chronic inflammation and fibrosis; increased stress response to endogenous and exogenous damage factors in hepatocytes, causing damage and inflammation to cell damage and inflammation, thus forming a vicious circle, which seriously affects the normal lipid metabolism process of the liver, and eventually hepatocyte fatty changes and physiological function damage occur. Some clinical studies have shown the prevalence of insulin resistance within hepatic fat in patients with NAFLD [7], and IR has been shown to be associated with abnormal NAFLD metabolism and type 2 diabetes. In addition, IR greatly increases the risk of impairment of fasting glucose and the development of type 2 diabetes mellitus. Sterol regulatory element activating protein (SREBP1C) is a major transcriptional regulator of lipid synthesis genes and regulates lipid synthesis by regulating the activity of enzymes related to lipogenesis, and in the case of hyperinsulinemia, sterol regulatory element activating protein SREBP1C is activated [8].There is a positive correlation i.e. a vicious circle between IR, hepatic ectopic fat accumulation and liver inflammation [9]. On the one

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hand, ectopic lipid accumulation in the liver leads to increased hepatic lipotoxicity, contributing to inflammation and IR. on the other hand, IR enhances lipotoxicity through uninhibited lipolysis, which in turn leads to a massive increase in pro-inflammatory markers such as tumor necrosis factor (TNF-α) and interleukin (IL-6), further aggravating IR and NAFLD [9]. In patients with NAFLD, intrahepatic inflammation is the most important prognostic determinant of liver disease progression and systemic inflammation associated with liver inflammation [10].

3. Acupuncture to modulate IR for NAFLD

Current studies have confirmed that acupuncture can treat IR by improving insulin sensitivity [11-12]. Some clinical experiments suggest that acupuncture can effectively treat NAFLD and has a better therapeutic effect on liver fat status, glucolipid metabolism, and IR. Several experiments conducted in NAFLD models have shown that acupuncture can inhibit the process of NAFLD by suppressing inflammation, reducing oxidative stress, and promoting hepatocyte lipid metabolism [13,14]. It has been reported [15,16] that acupuncture significantly reduces the level of about 70% of IR steady-state model assessment in IR-related diseases, and these results suggest that acupuncture can indeed be an effective treatment for NAFLD. the mechanism is mainly reflected in the following points: ① modulating central neurons ② regulating glycolipid metabolism ③ inhibiting inflammatory response and oxidative stress.

3.1 Modulation of central neurons by acupuncture

The hypothalamic center controls the appetite and energy metabolism of the whole body, while the hypothalamic neurons maintain the circulation of metabolites, so that the body mass and energy metabolism can be balanced [17]. Experimentally, we found that after acupuncture treatment with acupuncture points "Guan Yuan", "Zhong Gui", "Foot San Li" and "Feng Long", the body fat rate of IR rats decreased significantly. The mechanism may be that the hypothalamic TLR4/IκBα/NF-κB signaling pathway was downregulated by electroacupuncture, and the production of TNF-α, IL-1β and other inflammatory factors was reduced [18]. Another experiment suggested that electroacupuncture points such as "Foot San Li", "Nei Ting" and "Pancreatic Yu" could benignly regulate the central signaling pathway of IRS1/PI3K and effectively alleviate the central IR status of STZ rats [19]. The central IR state of STZ rats was effectively relieved [19]. In addition, the expression of subunit 85 of hypothalamic phosphatidylinositol 3 kinase (PI3K-p85) protein was reduced in obese rats after electroacupuncture at foot San Li and Qu Chi, which improved IR and decreased body mass [20]. There are two different nerves in the arcuate nucleus of the hypothalamus (ARC), Y neurons associated with appetite and POMC neurons associated with food suppression. In obese rats, after acupuncture points such as "Guan Yuan", "Zhong Gu", "Foot San Li" and "Feng Long", their body fat amount The expression of SIRT1 and POMC was synchronously regulated, indicating that electroacupuncture regulated the expression of SIRT1 to suppress appetite and improve body fat and metabolism in rats [21]. A domestic study found that electroacupuncture improved Leptin resistance, suppressed appetite, lowered blood and body fat, improved IR and maintained body energy balance by upregulating OB-Rb protein expression and increasing the affinity of leptin (Leptin) and leptin receptor (OB-Rb) [22], while another study also found that electroacupuncture reduced Leptin resistance by upregulating hypothalamic leptin mRNA and Ob- RbmRNA expression as a way to reduce serum TG and TC levels in obese rats [23].

3.2 Regulation of glycolipid metabolism by acupuncture

Elevated triglyceride (TG) and cholesterol (TC), along with elevated low-density lipoprotein (LDL-C) and reduced high-density lipoprotein (HDL-C), are called lipid metabolism disorders, and glucose transport protein 4 (GLUT4) plays an important role in maintaining blood glucose homeostasis. A team found that the expression of PGC-1α and UCP-1 protein in Epi-WAT was enhanced after electro-acupuncture in rats with "Tianshu" and "Foot Sanli", and the results showed that Lee's index was down-regulated and lipid metabolism was enhanced in rats [24]. enhanced [24]. In addition, it was found that after acupuncture treatment with acupuncture points such as "Hegu", "Quchi", "Foot Sanli" and "Sea of Blood", the PI3K-α and UCP-1 protein expressions were enhanced in IR mice. The expression levels of IRS-1, IRS-2 and GLUT4 proteins in the PI3K signaling pathway were significantly increased in IR mice after treatment with acupuncture points such as "He Gu", "Qu Ji", "Shu San Li" and "He Hai", and the symptoms of IR were relieved [25]. The efficacy of

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electro-acupuncture "belt vein" in down-regulating TG, TC and LDL-C levels and up-regulating HDL-C levels was demonstrated by the control of body mass, reduction of blood lipids and blood glucose, and improvement of metabolic disorders in IR rats [26]. After electroacupuncture of "Fenglong" and "Sanyinjiao" in IR rats, the results suggested that the expression of hepatic cholesterol regulatory element binding protein-1c and fatty acid synthase protein were downregulated, TG and TC synthesis were inhibited, and lipid accumulation and IR symptoms were reduced [27]. Another study demonstrated that electroacupuncture could improve lipid metabolism disorders in IR rats, which may be related to the reduction of fatty acid synthesis-related enzyme activity and regulation of AMPK/p38MAPK/pPARγ signaling pathway [28]. In another experiment, the body weight, blood lipids, and blood glucose of rats were observed by acupuncture at the "belt vein" point, and after 16 weeks of treatment, the body weight, FBG, FINS, HOMA-IR, TG, TC, and LDL-C levels of model rats were significantly reduced, which proved that stimulation of the "belt vein" point by electric acupuncture could effectively alleviate the disorder of IR. "acupuncture point, can effectively alleviate the metabolic disorders and reduce blood lipids and blood glucose in IR rats [29].

3.3 Inhibition of inflammatory response and oxidative stress by acupuncture

Inflammation and oxidative stress play a very important role in the progression of NAFLD. It has been shown that electroacupuncture points such as "Foot San Li", "Zhong Gui", "Guan Yuan" and "Feng Long" can improve the inflammatory response and insulin sensitivity in OIR rats. The mechanism is related to the expression of various pro-inflammatory and anti-inflammatory factors IL-10 in the fat [30]. Another study found that electro-acupuncture points such as "Zhonggui", "Guanyuan", "Feosanli" and "Fenglong" could improve the inflammatory response in OIR rats by down-regulating the expression of various pro-inflammatory factors and anti-inflammatory factors in adipose tissue [30]. The expression of TNF-α and IL-6 in the liver and adipose tissues inhibited the inflammatory response and indirectly affected the mRNA expression of ocludin and ZO-1 mRNA and protein expression in the intestinal tissues, restoring the intestinal barrier function and improving the IR status of obese rats [31]. Damaged hepatocytes can release inflammatory injury-related factors, activate the NF-κB pathway, and induce the production of pro-inflammatory cytokines such as TNF-α and ILs, which is a key step in the development of simple steatosis to NASH [32]. The mechanism is related to the inhibition of IKK/IKB/NF-κB signaling pathway activation, which reduces the "second strike" of inflammatory factors on the liver [33]. Excessive production of reactive oxygen species (ROS) in the body is a typical feature of obese patients, who are more susceptible to oxidative damage due to higher levels of intracellular oxidative stress than normals [34]. In IR rats treated with electroacupuncture, acupuncture points "Guan Yuan", "Foot San Li", "Zhong Gu" and "Feng Long" were used to treat the muscle tissue. The pro-oxidant radical-related enzymes and superoxide dismutase (SOD) activities in the tissues were enhanced, and the ROS content and malondialdehyde (MDA) in the liver were decreased, and oxygen radical damage was avoided and IR was reduced [35]. In an experiment, NALFD rats were divided into drug and electroacupuncture groups, and electroacupuncture points were taken from the back (both sides) of "Spleen Yu", "Diaphragm Yu" and "Kidney Yu". The results suggest that both drug intervention and electroacupuncture can reduce hepatic steatosis to different degrees, as shown by the decrease of MDA and increase of SOD activity, while the efficacy of acupuncture is higher in the rats [36], and electroacupuncture can also inhibit the expression of TNF-α and FFA in the liver of NALFD rats to avoid further hepatic steatosis in high-fat rats[37].

4. Factors affecting the efficacy of acupuncture

4.1 Acupoints own specificity and matching points

Regarding the specificity of the acupoints themselves, the hypolipidemic effect of the Fenglong point has now been confirmed. In addition, acupoint matching is an important part of acupuncture treatment. In a randomized controlled trial of buried acupuncture points in 100 patients with NAFLD, the main acupoints were Tianshu, Zhonggui, Fusanli, Liver Yu, and Kidney Yu, and the other acupoints were matched according to the condition: Zhangmen for liver depression and spleen deficiency, Fenglong for dampness and internal stagnation, Di Yu for phlegm and stasis, and Yanglingquan for dampness and heat, and the results showed that buried acupuncture had significant advantages over simple medication [38]. In another experiment, 60 rats were divided into five groups: normal (A), model (B), abdominal electro-acupuncture (C), lower limb electro-acupuncture (D), and specimen-assigned acupuncture points (E). The rats in group C were given "Guanyuan" and

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"Zhongbei", group D were given "Foot Sanli" and "Fenglong", and group E were given "Zhongbei" and "Guanyuan". "and "Fenglong" in group E. The results showed that the levels of TNF-α and IL-1β protein and mRNA decreased more significantly in rats in the specimen-acupuncture point group than in the other four groups [39]. In addition, NAFLD rats with acupuncture points "Tai Chong" and "Foot San Li" together with "Feng Long" and "San Yin Jiao" showed significant decreases in lipid metabolism, liver metabolism and mRNA levels. In rats with NAFLD, the degree of improvement in lipid metabolism, liver function, reduction in serum RBP4 and IL-18, and reduction in steatosis were significantly better than those in the non-acupuncture group [40, 41, 42]. In a comparison experiment between acupuncture points of Fenglong and other acupuncture points, serum LPL and HL levels of rats were observed, and the results showed that both acupuncture points of Fenglong and other acupuncture points could reduce LPL and HL levels, and compared with acupuncture points of Fenglong alone, the combination of acupuncture points of The results showed that the combination of "Guan Yuan" and "Neiguan" acupoints was more effective in reducing fat and avoiding lipopathy than the acupuncture of "Feng Long" alone [43]. This shows that the combination of acupuncture points and their mechanisms deserve further study.

4.2 Electroacupuncture stimulation parameters

Electroacupuncture is a combination of traditional acupuncture and modern technology, which greatly expands the therapeutic scope of acupuncture and improves the therapeutic effect. There are 3 types of electroacupuncture waveforms commonly used clinically: continuous being, intermittent wave, and sparse wave. Among them, the continuous wave with power less than 30Hz is sparse wave, which can improve blood circulation for short-term use, and above 30Hz is dense wave, which is used for pain relief and sedation. Changes in electroacupuncture parameters can affect the efficacy of treatment. The current electroacupuncture treatment NAFLD experiments mostly with parameters 2Hz, 1mA sparse wave for electroacupuncture. A study of electroacupuncture "Fenglong" lipid lowering found that electroacupuncture selected 100Hz, 30min needle retention, every other day once, for the regulation of TC, LDL-C best; selected 50Hz, needle retention 20min, twice a week, for the regulation of TG best [44]. With the change of electroacupuncture parameters, duration of needle retention, and time interval, it will have an effect on the regulation of lipids, blood glucose and other indicators, and its mechanism is worth further study and summary, and then explore the effect of electroacupuncture parameters on the indicators, symptoms, recurrence and adverse effects of NAFLD.

5. Summary

IR plays an important role in the pathogenesis of NAFLD, and acupuncture, as a characteristic therapy of Chinese medicine, can act on different targets and improve the metabolic disorders of the body through synergistic regulation of multiple pathways. Considering the advantages of acupuncture therapy, the efficacy of acupuncture in the treatment of NAFLD has been confirmed at home and abroad, following the meridian theory, dialectical acupuncture points, acupuncture techniques, and the progress of medical treatment, acupuncture is expected to become another major treatment for NAFLD. The effectiveness of acupuncture has been confirmed at home and abroad.

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