International Journal of General Medicine Dovepress

Open Access Full Text Article REVIEW

Acupuncture, a Promising Therapy for Insulin Resistance and Non-Alcoholic Fatty Liver Disease

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Abstract: Insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD) are representative metabolic diseases, and no pharmacological therapeutic strategies have been developed worldwide. In recent studies, acupuncture has increasingly been used as an integrative or complementary therapy for IR and NAFLD. In this review, we summarized 18 clinical trials and 25 animal studies to reveal the function and potential molecular mechanisms of acupuncture for IR and NAFLD treatment. We found that acupuncture can be a first-line treatment strategy for IR and has a positive therapeutic effect on NAFLD. Thus, this review provides clinicians with a deeper understanding of the scientific evidence for acupuncture treatment of IR and NAFLD. Finally, we highlighted three potential limitations of existing studies on acupuncture for the treatment of IR and NAFLD, including small sample sizes and inconsistent operating techniques.

Keywords: Traditional Chinese Medicine, acupuncture, insulin resistance, non-alcoholic fatty liver disease, metabolic health, alternative therapy

Introduction

Acupuncture, an indispensable and distinctly important part of Traditional Chinese Medicine (TCM), was first recorded in the *Yellow Emperor's Classic of Internal Medicine* which originated in China more than 3000 years ago. The traditional concept of acupuncture includes several forms of acupuncture, including needling, moxibustion, and cupping, while the chivalrous concept of acupuncture only refers to needling. Needling is the use of needles inserted into specific acupoints on the surface of the human body to achieve the effect of treatment and health care. Nearly 400 acupoints have been described worldwide, distributed in nearly 20 meridians (or channels of energy). In clinical settings, electroacupuncture (EA) and manual acupuncture (MA) are the two main forms of acupuncture widely used to treat various diseases.[1]

Acupuncture is one of the complementary treatments often chosen by patients,[2] and previous studies have shown that acupuncture is widely used for more than 70 diseases and conditions,[3] such as pain, anxiety disorders, depression, Alzheimer's disease, and vascular cognitive disorders. An increasing number of recent studies have demonstrated that acupuncture is highly effective in treating metabolic diseases including obesity, insulin resistance (IR), type 2 diabetes mellitus (T2DM), hyperlipidemia, and non-alcoholic fatty liver disease (NAFLD). However, there are no review has been reports of the simultaneous treatment of IR and NAFLD using acupuncture.

In the present review, we provide a systematic overview of the treatment of IR and NAFLD using acupuncture along with more recent advancements, providing more scientific evidence for the clinical treatment of IR and NAFLD. We then discuss the main signaling pathways involved in acupuncture in the treatment of IR and NAFLD. Finally, we discuss the potential limitations of the existing studies on the clinical application of acupuncture.

Received: 25 June 2024
Accepted: 20 October 2024
Published: 25 October 2024

Acupuncture for IR

IR is defined physiologically as a state of reduced responsiveness to high physiological insulin levels in insulin-targeted tissues. Clinically, the inability of insulin to increase glucose uptake and utilization triggers downstream metabolic actions in an individual as much as in the normal population.[4] In US, the adults 18 to 44 years of age, the prevalence of IR was approximately 40% from 2007 to 2018.[5] IR is considered a pathogenic driver of many modern diseases, including Alzheimer's disease, obesity, NAFLD, atherosclerosis, hypertension, T2DM, polycystic ovary syndrome (PCOS)[6] and sarcopenia.[7] Recently, IR-related diseases have become epidemics worldwide, representing a significant challenge to modern medicine in terms of patient treatment costs and escalating prevalence. There is no standard treatment for insulin resistance. In clinical practice, insulin resistance can be treated by changing lifestyle or using some hypoglycemic drugs, such as Biguanides, thiazolidinediones and GLP-1 receptor agonists. However, pharmacological treatments have limitations related to adverse drug effects, cost, and patient compliance. Currently, the therapeutic strategies of TCM and physical therapy for IR or IR related disease have received increasing attention, and a great number of clinical and animal studies have shown an effective treatment of acupuncture on homeostasis model assessment for insulin resistance (HOMA-IR), fasting blood glucose (FBG), fasting insulin (FINS), and 2-h postprandial blood glucose (2h-PBG).[8,9]

Clinical Trials of Acupuncture in IR Treatment

Pcos

Xiang et al performed a clinical study including 76 patients with PCOS-IR who underwent in vitro fertilization and embryo transfer, and these individuals were equally assigned to the EA and pseudo-acupuncture groups, respectively, for three menstrual cycles (25 min per time, twice a week). The data showed that EA therapy ameliorated the effects of phlegm-dampness syndrome and ovarian IR in patients.[10] Meanwhile, the mRNA levels of insulin receptor substrate (IRS)-1, phosphatidylinositol-3-kinase (PI3K), and GLUT4 in ovarian granulosa cells were significantly elevated after EA simulation.[10] The result indicated that this effect of acupuncture on PCOS-IR might be through the IRS1/PI3K/GLUT4 signaling pathway. Yang's study included 60 patients with PCOS-IR, who were randomly and evenly assigned to an acupuncture group and a control group: patients in the control group began to take letrozole and metformin orally on the third menstrual day, and patients in the acupuncture group were treated with acupuncture combined with Chinese medicine on the basis of the treatment of the control group. After treatment, the insulin level, blood sugar content, and HOMA-IR were lower than before treatment in both groups, with better results for insulin level and HOMA-IR improvement in the acupuncture group.[11] A controlled trial of EA and metformin performed by Yu et al showed that EA treatment may adjust dyslipidemia to improve IR and endocrine disorders in PCOS, and the effect is similar to that of metformin.[12] Dong et al reported a random clinical trial involving 44 PCOS patients in the true acupuncture and sham acupuncture groups, and these patients received a total of 16 weeks of treatment. The results showed a series of improvements in acupuncture treated group, including body weight, body mass index (BMI), hipline, waist-hip ratio (WHR), FBG, homeostatic model assessment of insulin sensitivity, visfatin, and serum HDL-c level,[13] suggesting that acupuncture may have a beneficial effect in the treatment of PCOS by improving glucose and lipid metabolism.

Wen et al designed a randomized clinical trial in 2015. Participants who were diagnosed with PCOS-IR were aged 18–40 years, with BMI ≥18.5 kg/m^2 and HOMA-IR ≥2.14. They were randomly assigned to receive acupuncture plus placebo, metformin plus sham acupuncture, or sham acupuncture plus placebo for four months. The results showed that the changes in HOMA-IR were −0.5 in the acupuncture group and −0.3 in sham acupuncture group compared with baseline. This indicated that there was no significant difference in the change in HOMA-IR between the acupuncture and sham acupuncture groups 4 months after the baseline visit.[14] In Wen's study, although acupuncture did not improve insulin sensitivity as effectively as metformin in women with PCOS-IR, the authors found that acupuncture treatment was better than metformin in improving glucose metabolism and had fewer side effects.[14]

Obesity

In patients with obesity and PCOS, acupuncture therapy for 6 months at the abdominal acupoint showed significant improvements in BMI, WHR, LDL-c, triglyceride (TG), total cholesterol (TC), FBG, 2-hour postprandial blood glucose, FINS, 2-hour postprandial blood insulin, and HOMA-IR.[15] Similar results have been reported by Shen et al.[16] In obesity,

a small pilot study, which included 16 obese women aged 30–52 years with BMI >30 kg/m, suggested that EA to either dorsal segmental points corresponding to the pancreas or to muscle points in all four limbs may exert a beneficial effect on glucose metabolism in obese women, as indicated by FBG testing; however, there was no effect on the glucose level in the treatment of EA on ear points.[17]

Diabetes

Zhao et al assigned 100 patients with prediabetes to metformin, acupuncture, and simple lifestyle intervention groups using the random number table method. After 12 weeks of continuous treatment, the authors found that acupuncture therapy downregulates body weight, FINS, IR, and leptin resistance while upregulating soluble leptin receptor content in prediabetic patients, suggesting that acupuncture plays a positive role in the treatment of prediabetes.[18] In diabetic patients, Firouzjaei et al found that metformin and acupuncture combined therapy was more effective in improving body weight, BMI, FBG, FINS, and HOMA index, as well as IL-6, TNF-α, leptin, adiponectin, GLP-1, resistin, serotonin, free fatty acids (FFAs), TG, LDL-c, HDL-c, and ceramides, than metformin alone. This suggests that acupuncture is an insulin sensitizer and can improve insulin sensitivity, possibly by reducing body weight and inflammation, while improving lipid metabolism and adipokines.[19] In T2DM patients, Cai et al showed that acupuncture at the Yishu, Feishu, and Pishu acupoints significantly reduced FBG levels and HOMA-IR compared to pre-treatment.[20] In T2DM patients complicated with by aspirin resistance, acupuncture combined with aspirin relieves insulin resistance and reduces blood glucose and lipid levels as well as the recurrence rate of cardiocerebrovascular events in the patients with T2DM.[21] Moreover, compared with rosiglitazone administration, EA therapy combined with rosiglitazone in newly diagnosed T2DM patients remarkably suppressed endogenous insulin secretion by improving IR via a mechanism involving a reduction in plasma FFAs.[22]

Animal Research of Acupuncture Treatment for IR

IR Amelioration

In PCOS-IR rats, Zhang et al found that acupuncture intervention corrected the pathological levels of serum follicle-stimulating hormone (FSH), estradiol, luteinizing hormone, testosterone, and FINS, thereby reducing IR.[23] In streptozotocin (STZ)-induced insulin-dependent diabetes mellitus rats, Shih-Liang Chang et al found that the EA stimulation at the "Zusanli" acupoints improves the intravenous glucose tolerance test (ivGTT) and the HOMA index, but the endogenous plasma insulin levels showed no change.[24] Lin et al used steroid-background rats induced by large doses of steroids (prednisolone) to obtain IR rats with higher HOMA indices and free fatty acid (FFA) levels. These IR-rats then received EA stimulation at the bilateral "Zusanli" acupoints. The authors found that EA stimulation improved glucose tolerance and insulin sensitivity by decreasing the serum FFA levels.[25] In STZ-induced IDDM rats, Yu-Chen Lee et al revealed the EA treatment on the "Zusanli" acupoint makes a hypoglycemic effect.[26]

Huang et al performed EA treatment in OLETF rats, and the data showed that FBG, FINS, C-peptide, and HOMA-IR were significantly ameliorated by EA administration.[27] In high-fat-diet (HFD)-induced obese rats, Li Wang et al found EA stimulation on "Zusanli", "Fenglong", "Sanyinjiao" and "Taichong" suppresses NAFLD induced upregulation of blood sugar, serum insulin, IR index[28] and lipid metabolism disorder.[29] Additionally, Shu et al showed that EA treatment improves obesity and IR by causing anorexia behavior.[30] Recently, Zhang et al found that the stimulation of the transcutaneous auricular vagus nerve using EA in Zucker diabetic fatty (ZDF) rats improves IR and ultimately obtains an anti-hyperglycemic effect by regulating plasma melatonin concentration.[31] Similarly, Dong et al reported that EA could reduce FBG and HOMA-IR levels and improve liver IR in ZDF rats.[32]

Molecular Mechanisms

Insulin action is initiated through the binding and subsequent activation of the insulin receptor in the cell plasma membrane. Once the insulin receptor is activated, it phosphorylates itself and several members of IRS. Insulin receptor–mediated phosphorylation of IRS proteins occurs on at least nine tyrosines within sequence motifs that recognize and activate PI3K and downstream protein kinases, resulting in the generation of polyphosphoinositides such as PI-(3,4,5) trisphosphate (PIP3).[33] Once recruited to the plasma membrane, PIP3-dependent kinase (PDK)-1 and mTORC2 phosphorylate and activate

protein kinase B (Akt), which can phosphorylate a number of substrates, including the GAP proteins RalGAPA, AS160, and TSC2, as well as FOXO proteins and GSK3.[33] Akt can also phosphorylate mTORC1, which in turn activates the SREBP pathway and promotes the expression of lipid synthesis-related genes such as SREBP1c and FAS.[33] Insulin reduces glucose production in the liver and increases the rate of glucose uptake in the skeletal muscle and adipose tissue. In skeletal muscle and adipose cells, the clearance of circulating glucose is dependent on insulin-stimulated translocation of GLUT4 isomers to the cell surface.[8]

As upstream molecules of insulin metabolism, IRS1, IRS2, and GLUT4 are activated after EA therapy in skeletal muscle and liver tissue.[25–27,34] The PI3K-AKT signaling pathway is midstream of insulin metabolism, and Zhang et al found that acupuncture intervention activated the expression of ovarian Akt and p-Akt proteins,[23] as well as AKT2 levels.[26,27] Huang revealed the PI3K-p85α protein were increased under EA stimulation, and indicated EA improves IR via the PI3K/Akt signaling pathway.[27,35] For downstream molecules of insulin metabolism, Liu et al found that the phosphorylation levels of AMPK, mTOR, and TSC2 decreased and p70S6K increased in the liver tissue of EA-treated ZDF rats.[34] Qing Shu et al showed the EA treatment upregulates the protein expression of hypothalamic SIRT1 and suppresses the acetylation level of FOXO1 in the hypothalamic arcuate nucleus, which decreased gene expression of NPY and increased that of pro-opiomelanocortin (POMC).[30,32] In addition, the expression of Srebp-1c and FAS in the liver of HFD-induced IR rats was reduced after EA administration.[29]

Acupuncture for NAFLD

NAFLD, a continuum of liver abnormalities from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), has emerged as a major cause of chronic liver disease in both children and adults worldwide, with an estimated global prevalence of 25.2% (range 22.1~28.6%).[36] In China, the overall incidence of NAFLD from 1999 to 2018 is as high as 32.9%.[37] Up to one–third of patients with NASH have increased liver–related mortality, attributed to progression to advanced fibrosis or cirrhosis and hepatocellular carcinoma (HCC).[36] In addition, NAFLD impacts on extrahepatic diseases, such as cardiovascular disease (CVD) and chronic kidney disease (CKD).[38] In the pathogenesis of NAFLD, people found the excessive lipid accumulation is the initial manifestation, and carries out the entire process from NAFL to NASH. IR, inflammation, and fibrosis are primary characteristics of NASH.[36] However, no NAFLD/NASH–specific pharmacological strategies have been approved by the FDA until February 2024, lifestyle modification, weight loss, and lipid-lowering and glucose-lowering medications are the default clinical treatment options.[36,39] Currently, although the FDA has approved a specific drug, Resmetirom, for the treatment of NASH, it is not widely used worldwide, and its efficacy and safety still need to be further observed. In recent years, growing evidence from animal and patient studies has shown that acupuncture is feasible for NAFLD/NASH therapy from improving lipid metabolism disorder and IR, inhibiting inflammatory, oxidative stress and endoplasmic reticulum stress.[40]

Clinical Trials of Acupuncture Administration for NAFLD Treatment

Draz et al designed a clinical trial that was conducted on 50 female patients with NAFLD aged 30–55 years. The participants were randomly divided into the EA stimulation and aerobic interval training groups. After six weeks of administration, the authors found that patients treated with EA showed a significant decrease in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and TG compared to those administered aerobic interval training.[41] Another randomized controlled trial involving 90 patients with obese-NAFLD, 45 patients in the acupuncture combined with lifestyle control group, and 45 patients in the lifestyle control group showed that the serum FINS, HOMA-IR, TC, and TG levels in the acupuncture group were significantly lower than those in the lifestyle control group after a 12 weeks' treatment, as well as waist circumference and WHR.[42] This study suggests that acupuncture combined with lifestyle control exhibits an effective therapeutic effect for obesity-NAFLD on hepatic fat status, glycolipid metabolism, IR, waist circumference, and WHR. Taha et al evaluated lipid profile response in patients with NAFLD who received EA stimulation at acupoints LR14, LR3, ST36, and GB34. They revealed that the levels of LDL-c, TC, and TG significantly decreased after six weeks of EA administration.[43] A meta-analysis of eight randomized controlled trials with 939 patients with NAFLD showed that acupuncture was superior to conventional medicine in improving overall clinical efficacy with satisfactory safety. Moreover, acupuncture administration is also beneficial for improving ALT,

AST, TC, TG, HDL-c, and LDL-c indices in individuals with NAFLD.[44] Recently, Zhao et al performed a randomized controlled pilot clinical trial performed by Jingjie Zhao et al was reported. The study included 60 patients with NASH who were assigned to the sham acupuncture or EA group in a 1:1 ratio and received 36 sessions of sham acupuncture or EA treatment over 12 weeks, followed by an additional 4 weeks of observation. The primary outcome showed that liver fat content was significantly decreased in the EA group compared to that in the sham group, as measured by magnetic resonance imaging of the proton density fat fraction. Furthermore, patients who received EA treatment showed significantly reduced body weight and BMI at week 16.[45]

Animal Study on Acupuncture Treatment of NAFLD

Acupuncture Improves Lipid Metabolism

When lipid metabolism is unbalanced, excess lipids accumulate in the liver, ultimately initiating the development of NAFLD. Thus, improving lipid metabolism to reduce steatosis is an effective strategy to prevent NAFLD progression. In an HFD-induced obese NAFLD rat model, Wang et al performed EA treatment on Daimai (GB26) rats once every other day. After 8 weeks of administration, the authors found that acupuncture therapy reduced body weight and abdominal fat accumulation and improved serum TG, TC, and liver malondialdehyde levels in abdominal obese NAFLD rats, as well as serum ALT and AST levels.[46] In methionine- and choline-deficient (MCD) diet-induced NAFLD mouse models, acupuncture administration reduced the accumulation of abdominal fat, reduced the absorption of lipids in the small intestine and blood lipids,[47] and ameliorated liver lipid droplets and NASH score.[48] In acupuncture-administered mice, the expression of microsomal triglyceride transfer protein, ApoB, and ApoC2 was downregulated[47] as well as that of hepatic Srebp1.[48] Similar results have been reported for HFD-induced NAFLD in rats.[49] Liu et al observed that EA administration not only improved hepatic histopathology, but also reversed the phosphorylation levels of AMPK, mTOR, and TSC2 in liver tissue.[34]

Acupuncture Ameliorates Hepatic Inflammatory Response

Zhi-Hua Zeng et al showed that the EA stimulation of bilateral "Pishu", "Shenshu", and "Geshu" could effectively down-regulated the liver FFA, malondialdehyde contents and TNFa expression, and notably increased hepatic SOD activity in NAFLD rats induced by HFD.[50] Excessive lipid deposition results in hepatic steatosis, making the liver vulnerable to proinflammatory cytokines and oxidative or endoplasmic reticulum stress, leading to hepatic inflammatory responses, injury, and fibrosis.[51] Therefore, effective anti-inflammatory therapy can improve liver function. Meng et al reported that hematoxylin and eosin (H&E) staining showed amelioration of inflammatory foci in the livers of acupuncture-treated mice, and the expression of IL1b, TNFa, and NF-κB was significantly decreased.[48] Wang et al found that administration of EA for 4 weeks inhibited the progression of NAFLD and decreased serum and hepatic Il18 levels.[28] Ma et al revealed the mechanism by which EA alleviates HFD-induced liver injury and inflammation in NAFLD rats by enhancing Sirt1 expression and inhibiting the NLRP3/NF-κB signaling pathway.[52] Chen et al found that the expression of inflammatory proteins, TLR4 and NF-κB, was reduced in the liver of patients with NAFLD and improved after acupuncture treatment.[53]

Acupuncture Inhibits Hepatic Oxidative Stress and Endoplasmic Reticulum Stress (ERS)

Meng et al found that the antioxidant enzyme-related genes glutathione peroxidase (GPx)-1, GPx2, and GPx3 significantly improved after acupuncture treatment, indicating that acupuncture represses the progression of NAFLD by reducing hepatic oxidative stress.[48] In Wang's study, the authors found that EA-treated NAFLD rats showed lower hepatic malondialdehyde levels and increased activity of hepatic total SOD and GPx, indicating that EA therapy inhibited oxidative stress in NAFLD models;[46] similar results were reported by Zhang et al a year later.[54] Yi Zhang et al reported the EA stimulation makes an amelioration of ERS in HFD-induced NAFLD rats as shown by decreased ERp57 and GRP78 expression after EA treatment.[55,56]

Acupuncture Improves Intestinal Microbiota

Recent studies have shown that intestinal microbiota and their metabolites have an important impact on the development of NASH.[38] Using 16S rRNA gene sequencing technology, Wang et al revealed that acupuncture administration altered

the intestinal microbiota of HFD-induced NAFLD rats, which showed that the abundance of Bacteroidales_S24-7_group, Prevotellaceae, Bacteroidaceae, Blautia, norank_f_Bacteroidales_S24-7_group, Bacteroides, and Prevotella_9 increased, and the Firmicutes to Bacteroidetes (F/B) ratio and Ruminococcaceae_UCG-014 were reduced,[57] suggesting the effect of acupuncture on the treatment of NAFLD through the acupuncture-gut-liver axis.

Conclusions and Future Directions

IR is involved in the development of multiple metabolic abnormalities such as NAFLD and NASH. Many previous studies have suggested a close relationship between IR and NAFLD, and the prevalence of NAFLD in T2DM patients is five times higher than that in non-T2DM patients. Meanwhile, IR is one of the key events in NASH development, supporting the existence of adipose tissue–liver crosstalk. Acupuncture is focused on the balance of "Qi", "Yin-Yang", and the "five elements" which is the three major principles of TCM in clinical practice. In the present review, we found that acupuncture treatment for IR mainly revised the key molecules of the insulin pathway (Figure 1), including IRS, Akt, FOXO, GSK3, SREBP1c, and FAS. In NAFLD, acupuncture improves the inflammatory response, lipid metabolism disorders, oxidative stress, ERS, and intestinal dysbacteria (Figure 1). Acupuncture can be a first-line treatment for patients with IR, as a large number of clinical trials have shown promising results in improving IR studies associated with a variety of conditions, such as PCOS, NAFLD, obesity, and T2DM. Although our review showed that acupuncture has positive results in the treatment of NAFLD, more large-scale and long-term randomized controlled trials with rigorous methodological inputs are needed to demonstrate the feasibility of acupuncture in NAFLD therapy because of the small number of clinical trials, insufficient sample size, and low methodological quality (Table 1).

There are four limitations of these studies contained in this review. Firstly, the standards for acupuncture methods were not unified. In traditional MA, when acupoints are fully activated, sensations of soreness, numbness, fullness, or heaviness called "De qi" are felt by patients. In the application of EA, although the acupoint stimulation time can be quantified, but "De qi" is unstable at the stimulated acupoints. In addition, the training levels of acupuncturists are various and the selection of acupoints during treatment cannot be standardized. In addition, the selection of acupuncture points is crucial in the course of disease treatment. In the past, people often questioned the importance and necessity of acupuncture points.[58] However, in this review, researchers used sham point as a control study, and the results showed that the sham point group did not receive effective treatment outcomes,[10,13,17,43] suggesting that the choice of acupoint was not blind. Thus, we suggest that unified acupuncture treatment guidelines for acupuncturists should be issued, and training bases for acupuncturists should be established. Secondly, acupuncture is widely used in clinical practice in clinical trials of IR and NAFLD therapy, but most of the studies involved only a single center, and the sample size was small. This leads to inaccuracies for the study results, for example, studies have also reported that acupuncture has no effect on IR. A randomized controlled trial of acupuncture in stable ischemic heart disease patients showed no differences in IR between the acupuncture treatment and control. [59] A study by Jessica M Garcia-Vivas et al showed that EA treatment had no significant effect on HOMA-IR in obese women compared to the sham acupuncture control group.[60] Therefore, Multi-center and large sample studies are necessary. Thirdly, both IR and NAFLD are chronic progressive diseases, but the lack of follow-up data in these studies makes it difficult to determine the long-term efficacy and safety of acupuncture intervention in IR and NAFLD. Thus, long-term regular acupuncture intervention studies are necessary. For example, a long-term acupuncture treatment may also be considered in the maintenance phase of a weight loss program to prevent recurrence in obese patient with IR or NAFLD. In addition, data from all phases of long-term treatment would provide a more comprehensive assessment of this complementary therapy. Finally, we found that the study of the molecular mechanisms of acupuncture treatment is insufficient, with most researchers detecting the expression of individual molecules lacking global transcriptomic demonstration. Therefore, a deeper exploration of the molecular mechanisms is warranted.

Acupuncture offers several potential advantages over conventional treatment, such as low cost, relatively few complications, and the possibility of individualized treatment. Acupuncture complications may be caused by inadequate needle disinfection and improper treatment implementation, which may lead to local pain, inflammation, or infection. However, in the hands of competent practitioners, acupuncture is a safe intervention.[6] Among 55,291 acupuncture treatments performed by medically trained acupuncturists, only 64 adverse events (0.12%) were recorded. All of these adverse events were mild and the most common were bruising, dizziness, sweating, malaise, and dermatitis.[61] However, more serious complications such as abscess

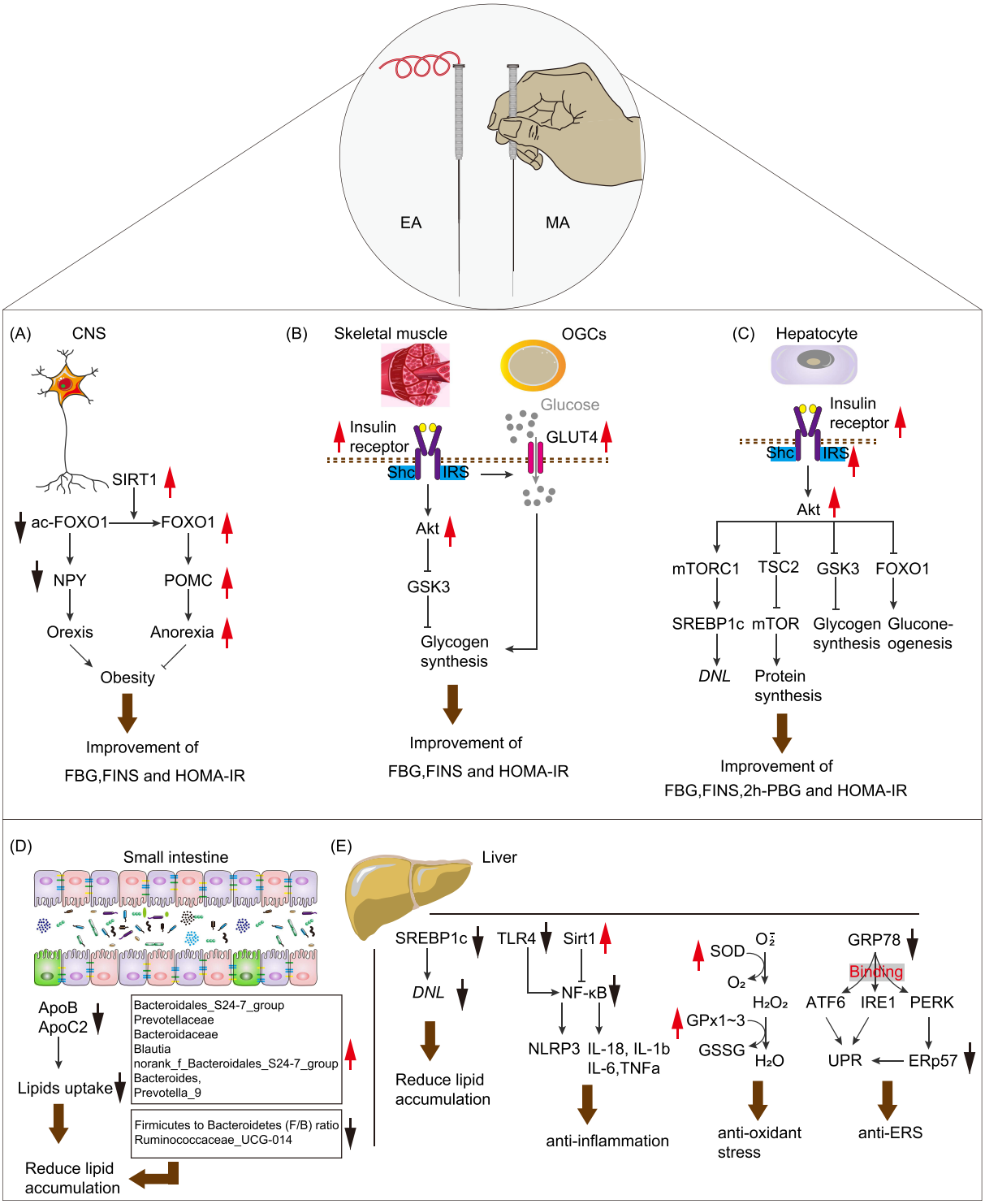

Figure 1 The potential mechanisms of acupuncture treatment in IR and NAFLD. (**A**) Acupuncture stimulation upregulated the protein expression of hypothalamic SIRT1 and suppressed the acetylation level of FOXO1 (ac-FOXO1) in the hypothalamic arcuate nucleus, which decreased gene expression of NPY and increased that of pro-opiomelanocortin (POMC). These molecular changes led to anorexia and weight loss, improved fasting blood glucose (FBG), fasting insulin (FINS) and homeostasis model assessment for insulin resistance (HOMA-IR). (**B**) In skeletal muscle and ovary granule cells (OGCs), acupuncture upregulated the expression of insulin receptor, GLUT4, and Akt, resulted in an increase of glycogen synthesis and improvement of FBG, FINS, and HOMA-IR. (**C**) In hepatocyte, acupuncture upregulates insulin receptor, IRS and Akt, resulting in an increase of *de novo* lipid synthesis (*DNL*), protein synthesis, glycogen synthesis and a decrease of gluconeogenesis, and finally improves FBG, FINS, 2-h postprandial blood glucose (2h-PBG), and HOMA-IR. (**D**) In small intestine, acupuncture administration downregulates the expression of apolipoprotein B (ApoB) and apolipoprotein C2 (ApoC2), and suppresses lipid absorption. In addition, the acupuncture makes an increase of Bacteroidales_S24-7_group, Prevotellaceae, Bacteroidaceae, Blautia, norank_f_Bacteroidales_S24-7_group, Bacteroides, and Prevotella_9, and decrease of the Firmicutes to Bacteroidetes (F/B) ratio and Ruminococcaceae_UCG-014 in NAFLD models. (**E**) Acupuncture therapy can improve liver lipid metabolism, anti-inflammatory, anti-oxidant, anti-endoplasmic reticulum stress (ERS), and ultimately improve NAFLD. Red arrows indicate upregulation, black arrows indicate downregulation. Abbreviations: EA, electroacupuncture; MA, manual acupuncture; CNS, central nervous system.

https://doi.org/10.2147/IJGM.S484260 DovePress

Table 1 Characteristics of the Clinical Trial Studies Cited in This Review

Study ID (First Author)	Disease	Group (Sample Size, n)	Acupuncture Type	Frequency	Acupoints	Outcome
Shan Xiang[10]	PCOS-IR	EA (38) vs sham acupuncture (38)	EA	25 min/time, twice a week for 3 menstrual cycles	Zhongwan (RN 12), Tianshu (ST 25), Daheng (SP 15), Daimai (GB 26), Qihai (CV 6), Guanyuan (CV 4), Xuehai (SP 10), Fenglong (ST 40), Zusanli (ST 36), and Yinlingquan (SP 9)	Ameliorate IR
Qidan Wen[14]	PCOS-IR	Acupuncture (114) vs metformin (114) vs sham acupuncture+placebo (114)	EA	30 min/time, 3 times a week for 4 months	EA, in the knee and abdomen; MA, in the hand and legs	Improve HOMA-IR; Improve glucose metabolism
Juan Yang[11]	PCOS-IR	Acupuncture+Chinese medicine (30) vs control (30)	MA, EA, Moxibustion	30 min/time, once every other day	MA: Guanyuan (CV 4), Qihai (CV 6), Zhongji (CV 3) and Xuehai (SP 10); EA: Qihai (CV 6) and Zhongji (CV 3), Xuehai (SP 10) and Yinlingquan (SP 9); Moxibustion: Guanyuan (CV 4) and Qihai (CV 6)	Ameliorate IR; Improve serum insulin; Improve blood glucose
Zhi-Ming Zhao[18]	Prediabetic patients	Metformin (35) vs acupuncture (35) vs simple lifestyle intervention (30)	MA	30 min/time, once every other day for 12 weeks	Feishu (BL 13), Pishu (BL 20), Weishu (BL 21), Shenshu (BL 23), Zusanli (ST 36) and Sanyinjiao (SP 6)	Reduce body weight; Downregulate FINS; Improve IR and leptin resistance
Hao-Xu Dong[13]	PCOS	EA (22) vs sham acupuncture (22)	EA	For 16 weeks	First set: Zhongji (CV 3), Qihai (CV 6), Guilai (ST 29), Sanyinjiao (SP 6), Yinlingquan (SP 9), Hegu (LI4) and Baihui (GV 20); Second set: Tianshu (ST 25), ST 29, CV 3, CV 6, SP 6, Taichong (LR 3), Neiguan (PC) 6 and GV 20	Lose weight; Improve BMI, WHR; Improve FBG; Improve HOMA-IR; Improve visfatin and HDLc
A Firouzjaei[19]	T2DM	EA+metformin (19) vs metformin (20)	EA	30 min/time, 10 times every other day for 3 weeks	Zhongwan (REN 12), Tianshu (ST 25), Zusanli (ST 36), Sanyinjiao (SP 6), Shuifen (REN 9), Hegu (LI 4), Daheng (SP 15), Shuidao (ST 28), Quchi (LI 11), Qihai (REN 6)	Improve glucose metabolism, lipid disorder and inflammation
Yuan-Qing Yang[21]	T2DM with aspirin resistance	Acupuncture+asprin (34) vs asprin (34)	MA	Once daily for 1 week	Zhongwan (CV 12), Zusanli (ST 36), Yinlingquan (SP 9), Hegu (LI 4)	Ameliorate IR; Reduce blood glucose and lipid
Ling-Yu Shen[16]	PCOS-obesity	EA (30) vs control (28)	EA, MA	20 min/time, 3 times a week for 12 weeks	EA (2 hz/100 hz, 4–8 mA), Daimai (GB 26) and Tianshu (ST 25); MA, Daheng (SP 15), Shenshu (BL 23), Ciliao (BL 32), Guilai (ST 29), Zulinqi (GB 41) and Waiguan (SJ 5)	Ameliorate IR; Improve FINS, HOMA-IR and waist circumference
Li-Qing Yu[12]	PCOS	EA (36) vs metformin (34)	EA	30 min/time, 3 times a week for 12 weeks	EA(2HZ), Zusanli (ST 36), Zhongwan (CV 12), Qihai (CV 6), Yishu (EX-B 3), Shenshu (BL 23), Pishu (BL 20), Ciliao (BL 32)	Ameliorate IR and dyslipidemia

Yan-Hua Zheng[15]	PCOS-obesity	EA (43) vs metformin (43)	MA	30 min/time, twice a week for 6 months	CV4, CV6, CV10, CV12, ST21, ST25, and ST28	Ameliorate IR; Reduce BMI and WHR; Improve glucose and lipid metabolism
Maria Belivani[17]	Obesity	EA on dorsal points (5) vs EA on limb points (6) vs EA on ear points (5)	EA	30 min/time	Dorsal: BL18, BL20, BL21 and BL23 bilaterally; Limb: LI10, LI11, ST36 and Zongping bilaterally; Ear: Lung and Heart points	Dorsal points and Limb points: beneficial effect on glucose metabolism; Ear points: no significance
Hui Cai[20]	T2DM	Acupuncture (40) vs glibenclamide (40)	MA	Once every other day for 12 weeks	Yishu (EX), Feishu (BL13) and Pishu (BL 20)	Ameliorate FBG; Improve HOMA-IR
Rong-Tsung Lin[22]	T2DM	Acupuncture+rosiglitazone (16) vs rosiglitazone (15)	EA	30 min/time, period was not mentioned	Zusanli (ST 36)	Improve glucose tolerance and insulin sensitivity; Decrease serum FFA level
Ramy Salama Draz[41]	NAFLD	EA (25) vs aerobic interval training (25)	EA	15 min/time, 3 times a week for 6 weeks	LR3, LR14, GB34, ST36	Ameliorate serum ALT, AST, TG, and CRP;
Can Dong[42]	Obese-NAFLD	Acupuncture+lifestyle control (45) vs lifestyle control (45)	MA, EA	30 min/time, 3 times a week for 12 weeks	MA: Zhongwan (CV 12), Quchi (LI 11), Shuifen (CV 9), Huaroumen (ST 24), Daheng (SP 15), Guanyuan (CV 4), Qihai (CV 6); EA: Huaroumen (ST 24) and Daheng (SP 15)	Reduce hepatic fat status and serum ALT; Reduce FINS, HOMA-IR, LDLc, TC and TG; Reduce BMI, and WHR
Mona Mohamed Taha[43]	NAFLD	EA (30) vs control (30)	EA	No mentioned	LR14, LR3, ST36, and GB34	Decrease serum LDL, TC and TG
Jingjie Zhao[45]	NASH	EA (30) vs control (30)	EA	30 min/time, 3 times a week for 12 weeks	CV12 (Zhongwan), CV4 (Guanyuan), bilateral ST25 (Tianshu), SP15 (Daheng), LV13 (Zhangmen), ST36 (Zusanli), SP6 (Sanyinjiao), LI4 (Hegu), and LV3 (Taichong)	Reduces relative liver fat content and serum AST; Improve BMI

Abbreviations: PCOS, polycystic ovary syndrome; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; EA, electroacupuncture; MA, manual acupuncture; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment for insulin resistance; BMI, body mass index; WHR, waist-hip-ratio; TC, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

https://doi.org/10.2147/IJGM.S484260 DovePress

formation, bacteremia, cardiac tamponade, spinal lesions, and pneumothorax have been reported in the literature, and these are limited to immunocompromised elderly subjects and patients with poorly controlled diabetes,[6] which suggests that we need to strengthen the nursing care during acupuncture treatment for these patients, such as strict management of acupuncture time and skin disinfection. Meanwhile, acupuncture should be avoided in elderly diabetic patients. Proper operation can avoid and correct the adverse reactions of acupuncture, acupuncturists should not only have good anatomical knowledge, but also have skilled operation skills to avoid inappropriate treatment.

Notably, four studies by Firouzjaei et al,[19,21,22,54] in our citation, used acupuncture combined with conventional treatment and achieved better therapeutic effects. Researchers have used acupuncture plus metformin, rosiglitazone, aspirin, and lifestyle modification, and all suggest that the combination provides more benefits and has a higher safety profile than metformin, rosiglitazone, aspirin, and lifestyle modification alone. Which indicated that incorporating acupuncture into a comprehensive treatment strategy is a potential and important option for metabolic diseases.

In conclusion, with the development of multicenter and multipopulation distribution studies, the therapeutic effects of acupuncture on IR and NAFLD will be more accurately demonstrated in the future. Meanwhile, with the development of advanced research technologies, the deeper molecular mechanisms of acupuncture therapy for IR and NAFLD will be revealed.

Acknowledgments

The authors acknowledge Dr. Dating Sun for editing the manuscript. Owing to space limitations, we apologize for not citing all the outstanding works in this field.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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