

Treatment for non-alcoholic steatohepatitis with type 2 diabetes by traditional Chinese medicine: a case report and experience

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Author contributions

Among the authors on the list, Xiang Cui played a guiding role in writing the article as the corresponding author. Jing Chang was responsible for collecting and sorting medical records, drafting and revising the article; Ling-Lan Liu participated in collecting case materials; Qian-Feng Wang also participated in collecting case materials.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

NAFLD, Non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MAFLD, metabolic-related fatty liver disease; T2DM, type 2 diabetes; TCM, traditional Chinese medicine; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; IR, insulin resistance; HD, hepatogenous diabetes.

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Abstract

Non-alcoholic fatty liver disease and type 2 diabetes are common comorbidities or target organ damage, which can lead to adverse metabolism and increased risk of cardiovascular and cerebrovascular diseases. In the management plan of non-alcoholic fatty liver disease and type 2 diabetes, there is no drug with significant efficacy or both. The dialectical idea of traditional Chinese medicine has a good curative effect and significant advantages in treating metabolic disorders. The author now reviewed a case of non-alcoholic steatohepatitis combined with type 2 diabetes. In this case, the method of invigorating the spleen and eliminating turbidity was effective, which effectively prevented the progression of liver disease in the patient, and T2DM was alleviated by maintaining within the standard range after the use of insulin was stopped. It can be said that “killing two birds with one stone”, more fully reflects the advantages of traditional Chinese medicine in the integrated treatment of metabolic-related diseases.

Keywords: traditional Chinese medicine; invigorating spleen and removing turbidity; metabolism-related fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to a group of clinical syndromes, including non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and liver cancer, except for those induced by excessive alcohol consumption or apparent liver injury factors [1]. Given its similar pathogenesis with multiple metabolic disorders, the international expert group recommended in early 2020 to redefine NAFLD as metabolic-related fatty liver disease (MAFLD). Specifically, histological (liver tissue biopsy), imaging, and blood biomarker evidence of liver fat accumulation (hepatocyte steatosis), combined with one of the following conditions: overweight/obesity, type 2 diabetes (T2DM), and metabolic dysfunction [2]. The name of MAFLD is not only the change of initials but also gives us the biggest thinking and enlightenment: how to integrate the treatment of various metabolic-related diseases from the holistic view of TCM [3]. Guided by the holistic view and considering the multi-level and multi-target characteristics of TCM, TCM has unique advantages in integrating the treatment of metabolic diseases. It is worth thinking about how to use this advantage to treat this disease better. In recent years, the diagnosis and treatment center of fatty liver and obesity in our hospital has adopted the “four-dimensional integration” integrated defense and treatment mode combined with spleen treatment of metabolic diseases for nearly 10000 cases of MAFLD, with remarkable clinical effects [4, 5]. One of the classic cases of NASH combined with T2DM was analyzed retrospectively and reported as follows to provide ideas for treating such diseases.

Case profile

The patient is a 48-year-old man born in Ankang, Shaanxi Province. He first visited the Treatment Center for Fatty Liver and Obesity of our hospital on September 17, 2021, complaining of “body fatigue, polydipsia, polyuria, blurred vision, and liver discomfort for more than two months.” He described that he likes greasy food in his daily diet and does not enjoy exercise. The physical examination results were: height 170 cm, weight 74 kg, and body mass index (BMI) 25.6 kg/m² (overweight); His tongue was dark with a greasy coating and obvious tooth marks. His pulse was wiry and thin. The accessory examination included liver function: aspartate transaminase (AST) 178 U/L, alanine transaminase (ALT) 215 U/L; Liver CT: moderate fatty liver (liver/spleen 0.67) (Figure 1); FibroScan test: CAP 291 dB/m, E 14.3 kPa; fasting glucose: glucose 17.08 mmol/L, fructosamine 3.98 mmol/L, urine routine: glucose with 4 plus sign, blood lipid, renal function, hepatitis B series, and alpha-fetoprotein were normal. Western medicine diagnosis: NASH combined with type 2 diabetes. TCM diagnosis: (1) GanPi (spleen-deficiency, phlegm blocking, blood stasis); (2) PiDan (abdominal fullness and internal heat, phlegm damp trapped spleen). According to the patient's examination results, we take TCM combined injection insulin treatment. Insulin therapy was given to control fasting blood glucose, and TCM was used to invigorate the spleen and eliminate turbidity for NASH treatment. The TCM prescriptions were applied as follows: *Puerariae Radix* 30 g, *Astragali Radix* 15 g, *Curcumae Radix* 15 g, *Poria cocos* 15 g, *Smilacis Glabrae Rhizoma* 15 g, *Alismatis Rhizoma* 10 g, charred *Crataegi Fructus* 10 g, *Sargassum* 10 g, fired *Cassiae Semen* 10 g, *Nelumbinis Folium* 20 g, *Nelumbinis Folium* 20 g, *Phyllanthus urinaria* 20 g, *Polygoni Cuspidati Rhizoma* 10 g, *Semen Benincasae* 10 g, a total of 10 doses, one dose per day, two times a day, be decocted in 400 mL water for an oral dose. The patient was asked to discontinue other liver-protecting drugs. We guided the patient to establish a reasonable dietary pattern, enhanced aerobic exercise, and appropriate physical exercise and told the patient to adjust his emotions and maintain a happy mood.

The second diagnosis was on September 28, 2021. The patient had the chief complaints were dry mouth, no appetite, and abdominal distension. His tongue was a dark color, with tooth marks. Liver function: AST 98 U/L, ALT 92 U/L; fasting glucose: glucose 6.03

mmol/L, fructosamine 2.17 mmol/L; On the basis of the original prescription, add *Curcuma zedoaria*, *Sparganii Rhizoma*, *Atractylodis Macrocephalae Rhizoma* stir-fried with bran, removed *Curcumae Radix*, *Semen Benincasae*. A total of 30 doses, daily 1 agent, two times a day, be decocted in 400 mL water for an oral dose. Besides, 10 doses of insulin glargine injection and insulin lispro injection (3 mL: 300 IU) were administered subcutaneously.

The third diagnosis was on October 28, 2021. The patient showed no discomfort. His main clinical manifestation characteristics were dark tongue with tooth marks, wiry and thin pulse. Liver function: AST 106 U/L, ALT 109 U/L; fasting glucose: glucose 4.93 mmol/L, fructosamine 1.99 mmol/L; The same decoction was prescribed for another 15 doses. Besides, 10 doses of insulin glargine injection and insulin lispro injection (3 mL: 300 IU) were administered subcutaneously.

The fourth diagnosis was on November 15, 2021. The patient indicated no apparent discomfort. His tongue was pale with tooth marks. Liver function: AST 77 U/L, ALT 60 U/L; fasting glucose: glucose 5.37 mmol/L, fructosamine 1.92 mmol/L; Glycated hemoglobin value 8.3%. Based on the last prescription, Chinese honeylocust spine was added, and bran fried *Rhizoma atractylodis macrocephalae* was removed, and 15 doses were taken continuously. Besides, 10 doses of insulin glargine injection (3 mL: 300 IU) were administered subcutaneously.

The fifth diagnosis On December 6, 2021, the patient did not complain of discomfort. His tongue is dim. Liver function: AST 85 U/L, ALT 71 U/L; Glycosylated hemoglobin value was 6.0%. The last prescription continued to take 15 doses. Besides, 10 doses of insulin glargine injection (3 mL: 300 IU) were administered subcutaneously.

The sixth diagnosis On December 30, 2021, the patient exhibited no discomfort. His tongue was pale, with a thin and white tongue coating. The symptom of tooth marks were reduced. His pulse was wiry and thin. Liver CT: (liver/spleen 1.01); hepatic function: AST 68 U/L, ALT 45 U/L; fasting glucose: glucose 4.99 mmol/L, fructosamine 1.60 mmol/L; The above indicators returned to normal. On the basis of the original prescription, added vinegar-processing *Bupleuri Radix* 6 g, *Citri Reticulatae Pericarpium* 15 g, *Taxilli Herba* 15 g, removed *Curcumae Radix*, *Astragali Radix*, *Curcumae Rhizoma*, *Sparganii Rhizoma*, *Laminariae Thallus Eckloniae Thallus*, *Sedi Herba*, *Phyllanthus urinaria*, 15 doses followed.

Seventh diagnosis On April 26, 2022, The patient self-reported that he had stopped using insulin for more than two months without feeling discomfort. CT value: liver/spleen > 1.0; Liver function: AST 46 U/L, ALT 54 U/L; fasting glucose: glucose 5.36 mmol/L, fructosamine 1.75 mmol/L; glycosylated hemoglobin value 5.6%. Liver function and blood glucose were within the standard range.

After more than three months of treatment with traditional Chinese medicine combined with insulin, the patient's uncomfortable symptoms disappeared, and serum transaminases (Table 1) and blood glucose (Table 2) showed a decreasing trend (Figure 1–2). CT values of liver imaging showed disappearance of fatty liver (Figure 3B). The efficacy evaluation indexes were within the standard range, and the evaluation of efficacy was stable after three months of follow-up (Figure 3C).

Discussion

Obesity and insulin resistance (IR) are the common risk factors for NAFLD and type 2 diabetes mellitus (T2DM). Studies have shown that excessive lipid accumulation can trigger IR, which leads to abnormal glucose and lipid metabolism, thus entering a vicious cycle [6]. Ultimately, NAFLD, T2DM, and cardiovascular disease occur and develop [7–8]. Weight loss and abdominal circumference reduction can not only improve the glucose metabolism of type 2 diabetic patients but also effectively reduce liver fat deposition. Therefore, in many management programs for NAFLD with T2DM, lifestyle interventions such as diet control and exercise are preferred. However, it is not easy to maintain weight loss by adjusting lifestyle alone. In clinical practice, managing NAFLD patients with T2DM is primarily

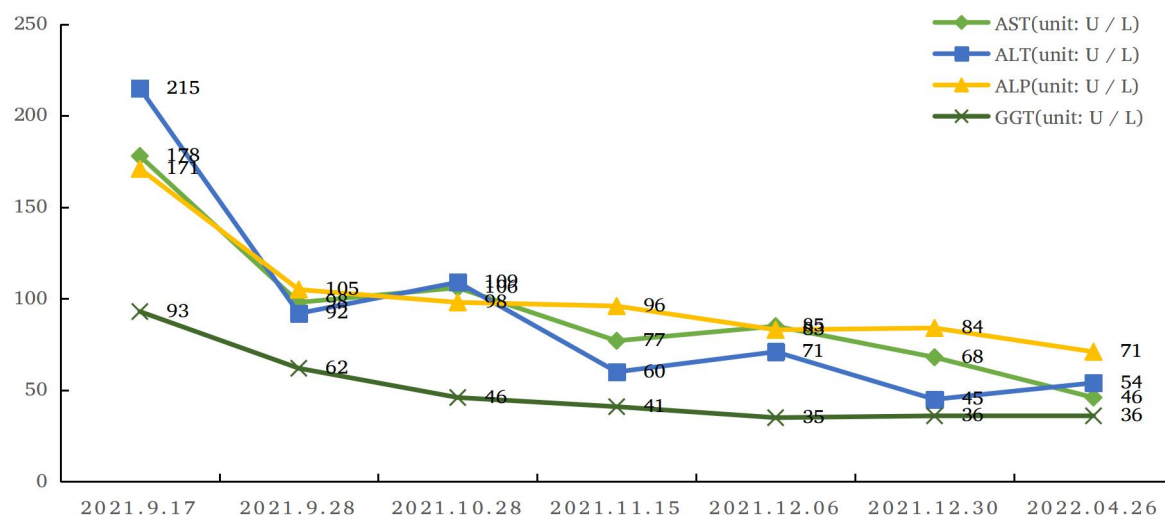


Figure 1 The change of transaminase after treatment

Table 1 The level of transaminase after treatment with traditional Chinese medicine

Time	AST (unit: U/L)	ALT (unit: U/L)	ALP (unit: U/L)	GGT (unit: U/L)	AST/ALT
2021.09.17	178	215	171	93	0.8
2021.09.28	98	92	105	62	1.1
2021.10.28	106	109	98	46	1.0
2021.11.15	77	60	96	41	1.3
2021.12.06	85	71	83	35	1.2
2021.12.30	68	45	84	36	1.5
2022.04.26	46	54	71	36	0.9

Table 2 FBG and GHb level after treatment with traditional Chinese medicine

Time	GLU (unit: mmol/L)	GSP (unit: mmol/L)	HbA1C (unit: mmol/L)
2021.09.17	17.08	3.98	/
2021.09.28	6.03	2.17	/
2021.10.28	4.93	1.99	8.3%
2021.11.15	5.37	1.92	/
2021.12.06	5.24	1.69	6.0%
2021.12.30	4.99	1.60	/
2022.04.26	5.36	1.75	5.6%

based on combining lifestyle drugs [9]. The pathogenesis of NAFLD is complex, and there are currently no approved drugs for treating the stage of NASH, despite years of research worldwide [10]. In contrast, for its concomitant T2DM, insulin administration is one of the essential means of intensive treatment [11].

According to the consensus of the international expert group on MAFLD, this case belongs to a metabolic disorder including two diseases, and according to its clinical characteristics, Chinese medicine classifies its central disease NASH as “GanPi” (spleen-deficiency, phlegm blocking, blood stasis) [12] and T2DM combined with NASH as “PiDan” (abdominal fullness and internal heat, phlegm damp trapped spleen) [13]. “Both are closely related to the impaired function of the spleen and stomach.” In the “Treatise on Febrile and

Miscellaneous Disease”, it is said that “when we see the disease of the liver, we know that the liver transmits the spleen, so we must first strengthen the spleen.” However, the disease is located in the liver, and the key to the disease mechanism is in the spleen. In the theory of Chinese medicine, the spleen distributes nutrients to the whole body and regulates the qi (Qi is the most basic substance that makes up the human body and sustains its vital activities) ascending and descending, which is fundamental to maintaining the balance of material and energy metabolism in the body. If the spleen is deficient, the qi (Qi is the most basic substance that makes up the human body and sustains its vital activities) becomes unregulated. The dispersal of nutrients is weak, resulting in the internal production of phlegm, dampness, heat, silt, and other pathological products, which

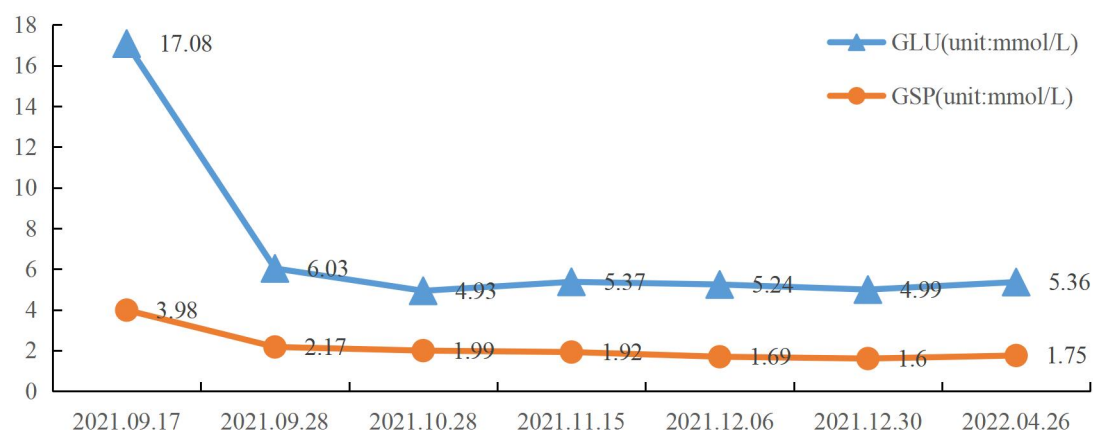


Figure 2 The change of after treatment

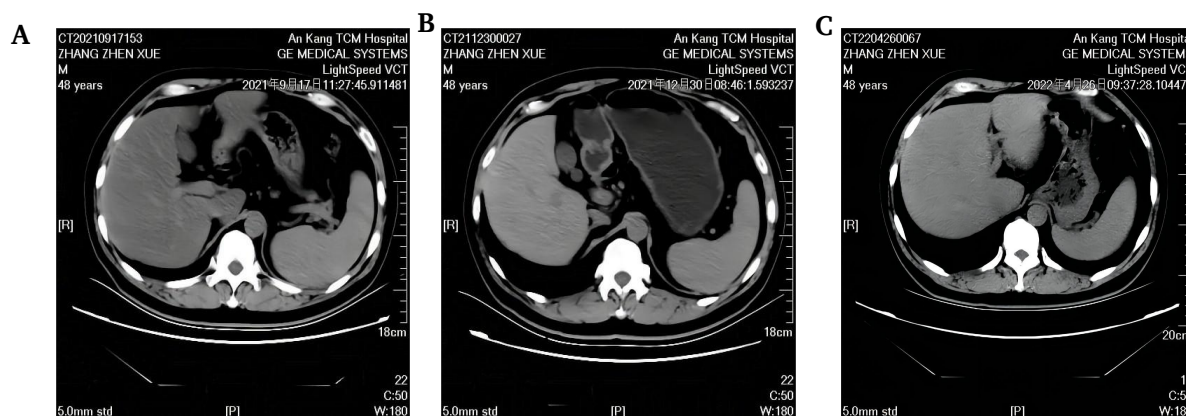


Figure 3 (A) Image before treatment. (B) Image after treatment. (C) Image follow-up review.

accumulate in the liver and become **GanPi** (spleen-deficiency, phlegm blocking, blood stasis); if the silt is blocked in the veins, it leads to abnormal blood glucose, blood lipids, and blood pressure; based on this, the author believes that “spleen dysfunction, turbidity and toxicity endogeny, weak dispersal of essence and disorder of **qi** (**Qi is the most basic substance that makes up the human body and sustains its vital activities**)” is the basic pathogenesis of MAFLD, and “strengthening the spleen to help transportation, raising the yang and resolving turbidity (toxicity)” is the primary treatment for metabolic diseases, referred to as the method of invigorating the spleen and dissolving turbidity [14]. The prescription used in this case is based on this method, with flexible tailoring according to the changes in the symptom. *Puerariae Radix* and *Astragali Radix* are the sovereign herbs at the beginning of the disease. *Puerariae Radix* elevates the spleen-**yang** (The transportation function of spleen and yang **qi**, which plays a warming role in the process of transportation, are the reflection of human yang **qi** in spleen function.), *Astragali Radix* nourishes the spleen **qi** (**Qi is the most basic substance that makes up the human body and sustains its vital activities**), and the two herbs work together to normalize the **qi** (**Qi is the most basic substance that makes up the human body and sustains its vital activities**) flow and the distribution of fluids. The minister drugs including *Poria cocos*, *Alismatis Rhizoma*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Curcuma Radix*, and so on, *Poria cocos* invigorates the spleen and excreting dampness, with *Alismatis Rhizoma* can enhance the effect of clearing dampness so that dampness is not gathered, phlegm is not generated; *Curcuma Radix* promoting **qi** (**Qi is the most basic substance that makes up the human body and sustains its vital activities**) to active blood, with *Salviae Miltiorrhizae Radix et Rhizoma* to enhance the effect

of promoting blood circulation and removing stasis; *Nelumbinis Folium*, *Cassiae Semen* etc. as adjuvant drugs, *Nelumbinis Folium* wakes the spleen-**yang** (The transportation function of spleen and yang **qi**, which plays a warming role in the process of transportation, are the reflection of human yang **qi** in spleen function.), *Cassiae Semen* clear the liver and moisten intestines, leading the medicine into the liver and large intestine. Then, combined with the signs of the tongue and pulse, *Curcuma Rhizoma* and *Sparganii Rhizoma* were added to invigorate blood circulation and resolve blood stasis, and *Atractylodis Macrocephalae Rhizoma* was added to strengthen the spleen function. After the normalization of the indicators, strengthening the vital and dispelling the evil, vinegar-processing *Bupleuri Radix* and *Citri Reticulatae Pericarpium* were added to smooth liver-**qi** (**Qi is the most basic substance that makes up the human body and sustains its vital activities**), raise the yang **qi** (Yang **qi** refers to a kind of energy, which is the prime motivity of material metabolism and physiological function of human body), and regulate the middle warmer. Adding *Taxilli Herba* nourishes the liver and kidney and strengthens the muscles and bones.

During the treatment process, it was worth noting that the patient reported that he had stopped the insulin by himself; the fasting blood glucose and glycated hemoglobin were normal on recheck, so he continued to stop this medicine after three months of follow-up, the fasting blood glucose was normal, and the glycated hemoglobin value was < 6.5%, which had achieved the criteria for remission of T2DM [15]. Therefore, combining the characteristics of this patient before and after the treatment, we tend to consider this case as hepatogenous diabetes (HD) secondary to long-term nonalcoholic steatohepatitis [16]. Although the concept of HD has been proposed for a long time,

there is no international guideline or consensus for the diagnosis of this disease. The mainstream view mostly considers HD to occur based on severe liver disease such as cirrhosis [17], while HD based on fatty liver disease is not given much attention. In Chinese medicine, the name of HD is “liver elimination”. It is believed that its pathogenesis is mainly in the liver, so the treatment of the liver should be the main focus, and the transmission of liver disease to the spleen is the basic pathogenesis of the transformation of liver disease to HD [18]. Based on the holistic dialectical thinking of TCM and the idea of “unifying all diseases with the disease mechanism”, it is worth exploring whether “strengthening the spleen and helping transportation, raising yang qi (Yang qi refers to a kind of energy, which is the prime motivity of material metabolism and physiological function of human body), and resolving turbidity” can be taken as the basic treatment for HD.

This case will continue to be followed up, and the patient will be informed to continue to consolidate and strengthen compliance with lifestyle interventions during treatment, which is worthy of further exploration and study.

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