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*Original Article*

# Effects of combination treatment of metformin and hawthorn in patients with prediabetes complicated by nonalcoholic fatty liver disease

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**Abstract:** The study aimed to investigate the effect of combination treatment of metformin and hawthorn in patients with prediabetes complicated by nonalcoholic fatty liver disease (NAFLD). Eighty-four patients with prediabetes complicated by NAFLD were randomly divided into the treatment group (n = 42, treated with a combination of metformin and Hawthorn), and the control group (n = 42, treated with metformin alone). The BMI, FPG, FIN, 2hPG, HbA1c, TG, TC, HOMA-IR, ALT, AST, hs-CRP and liver ultrasound were measured in each group before and after 24 weeks of treatment. Compared with before treatment, BMI, HbA1c, FPG, 2hPG, FIN, HOMA-IR, TG, TC, ALT and hs-CRP were significantly reduced after treatment in both groups ($P<0.05$ or $P<0.01$). After treatment, BMI, HbA1c, FPG, 2hPG, TG and hs-CRP in the treatment group were significantly decreased compared to that in the control group ($P<0.05$ or $P<0.01$). Doppler ultrasound showed that compared with the control group, the degree of liver steatosis was significantly reduced in the treatment group ($P<0.05$). Combination treatment of metformin and Hawthorn could significantly reduce body weight, insulin resistance, and hs-CRP levels, and regulate glucolipid metabolism. Thus combination treatment of metformin and hawthorn is more effective in treating patients with prediabetes complicated by NAFLD.

**Keywords:** Metformin, hawthorn, prediabetes, nonalcoholic fatty liver disease

## Introduction

In recent years, the prevalence of diabetes has reached 11.6% of adults aged 18 years or older in China. The prevalence rate of prediabetes is 50.1%. Adults who are overweight have higher rates of diabetes [1]. The prevalence of nonalcoholic fatty liver disease (NAFLD) in adults is estimated to be 20% to 33%. Patients with NAFLD are more likely to develop prediabetes or even type 2 diabetes (T2DM). The prevalence of prediabetes in patients with NAFLD is higher than that of the general population. There is a mutual relationship between hyperglycemia and NAFLD. Prevention and treatment of prediabetes and NAFLD has become a research hotspot currently. Most studies show that metformin can reduce insulin resistance, but has no significant effect on hepatic enzymes and pathological changes in liver [2, 3]. The effect of hawthorn on the treatment and prevention of fatty liver and pre-diabetes have been reported [4, 5]. In the present study, the clinical efficacy of the combination of metformin and hawthorn was investigated for treating patients with prediabetes complicated by NAFLD. These data demonstrate changes in the high-sensitivity C-reactive protein (hs-CRP) before and after combination treatment.

## Subjects and method

### *Subjects*

A total of 84 patients with prediabetes complicated by NAFLD who were admitted to our hospital from January, 2015 to December, 2016 were included in this study. All patients were divided into a control group (treated with metformin alone) and a treatment group (treated with combination of metformin and hawthorn), with 42 patients in each group. The control

group included 24 males and 18 females ranging in age from 22 to 59 years old (The average age was 43.33±10.32). The treatment group included 25 males and 17 females ranging in age from 22 to 59 years old (The average age was 42.36±9.90). All patients had prediabetes and NAFLD for more than half a year. There was no significant difference between the two groups in terms of general data ($P$>0.05). The study was approved by the Ethics Committee of our Hospital. Written informed consent was obtained from each subject.

Inclusion criteria were: Patients with prediabetes and NAFLD, aged 20-59 years; ALT and AST levels ≤2 times the upper limit of normal; patients who signed the written informed consent.

Exclusion criteria were: Patients with alcoholic liver disease, autoimmune liver disease, hyperacidity, gastritis, gastric ulcers, reflux gastritis, reflux esophagitis; and those with severe systemic disease (i.e. diseases of heart, liver, lung, kidney and blood, serious infections, psychotic disorders, connective tissue diseases); 2) patients who used of drugs affecting systemic glucose metabolism such as hormone within three months prior to the study. 3) Preparing pregnant, pregnant and lactating women. 4) Patients who couldn't cooperate.

*Diagnostic criteria*

Diagnosis of prediabetes was made according to the Chinese Guideline for Diabetes Prevention and Treatment (2010). Prediabetes is known as impaired glucose metabolism, including impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT). 1) IFG: fasting blood glucose ≥6.1 mmol/L and <7.0 mmol/L, two-hour oral glucose tolerance test (OGTT) glucose <7.8 mmol/L. 2) IGT: fasting blood glucose <6.1 mmol/L; two-hour OGTT glucose ≥7.8 mmol/L and <11.1 mmol/L. 3) IFG+IGT: fasting blood glucose ≥6.1 mmol/L and <7.0 mmol/L, two-hour OGTT glucose ≥7.8 mmol/L and <11.1 mmol/L. NAFLD was diagnosed according to the guidelines for the diagnosis and management of non-alcoholic fatty liver disease issued by the Chinese Liver Disease Association of Chinese Medical Association. The severity of NAFLD was assessed based on detection in ultrasound images.

*Method*

All patients from the control and treatment groups received health education, including healthy eating (low-fat diets), regular physical exercise, but no specific dietary approaches were made. Patients in the control group was treated with metformin (Shanghai Shiguibao Medicine Co., Ltd., China), the dose of metformin was taken as one 500 mg tablet orally three times daily. In addition to metformin administration, patients in the treatment group also received dietotherapy with hawthorn. A dose of 30 g hawthorn (net hawthorn, purchased from Sinopharm Group Co., Ltd., China, produced in Shandong province) was taken, after an 30 minute soak by adding 400 ml water, then the mixture was fully boiled over a quick fire (high heat), and then simmered over slow fire (low heat) for 30 minutes. After turning down the fire, and standing for 1 hour, the water decoction of hawthorn were filtered and collected in a cup. Patients received 1/3 cup of the water decoction three times a day after meal. All patients received 24-week duration of treatment. The treatments were discontinued if liver function tests exceed 3 times the upper limit of normal.

*Observation indexes*

Both oral glucose tolerance test (OGTT) and insulin release test (IRT) were performed in patients of two group before and 24 weeks after treatment. Serum samples were collected, and the glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting insulin (FIN), 2-hour postprandial plasma glucose (2hPG), triglyceride (TG), cholesterol (TC), and ALT were measured using biochemical immunity conjunctedly machine (Architect Ci16200, Abbott). hs-CRP was determined using turbidimetric immunoassay. Abdominal ultrasound was performed with GE vivid-E9 ultrasound system by a radiologist. The insulin resistance index (HOMA-IR) was then calculated using the following formula: HOMA-IR = FPG × FIN/22.5. Height and body weight were measured and BMI was calculated. During treatment, adverse reactions in patients of the two groups were observed and recorded.

*Evaluation of treatment efficacy*

Treatment efficacy was evaluated by abdominal Doppler ultrasound. Markedly effective was

**Table 1.** Comparison of changes in biochemical parameters in patients between two groups (n = 42, mean ± SD)

| Group | HbA1c (%) | FPG (mmol/L) | 2hPG (mmol/L) | FIN (mIU/L) | HOMA-IR | TG (mmol/L) | TC (mmol/L) | ALT (U/L) | AST (U/L) | BMI (kg/m$^2$) | hs-CRP (mg/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Control group | | | | | | | | | | | |
| Before treatment | 6.25±0.39 | 6.21±0.44 | 9.27±1.55 | 11.94±6.00 | 3.29±1.70 | 2.66±1.37 | 5.67±0.84 | 62.38±22.04 | 43.21±18.90 | 28.16±3.08 | 2.07±1.43 |
| After treatment | 5.60±0.54 | 5.55±0.78 | 7.61±1.44 | 8.24±5.37 | 2.03±1.37 | 2.11±1.09 | 4.73±0.90 | 53.45±22.54 | 37.95±15.52 | 26.32±2.86 | 1.72±1.19 |
| Treatment group | | | | | | | | | | | |
| Before treatment | 6.22±0.37 | 6.17±0.42 | 9.12±1.45 | 12.35±8.18 | 3.36±2.17 | 2.69±1.34 | 5.57±0.81 | 58.62±21.27 | 41.60±19.18 | 28.04±3.76 | 2.17±1.56 |
| After treatment | 5.21±0.70 | 5.22±0.72 | 7.01±1.18 | 6.48±6.65 | 1.46±1.33 | 1.66±0.91 | 4.37±0.97 | 44.10±21.18 | 33.93±16.14 | 25.04±3.01 | 1.11±0.83 |
| *t*1 Value | 0.286 | 0.463 | 0.479 | 0.262 | 0.146 | 0.09 | 0.554 | 0.796 | 0.39 | 0.162 | -0.267 |
| *P*1 value | 0.775 | 0.644 | 0.633 | 0.794 | 0.884 | 0.929 | 0.581 | 0.428 | 0.698 | 0.871 | 0.79 |
| *t*2 value | 6.260 | 4.817 | 5.083 | 2.976 | 3.762 | 2.041 | 4.968 | 1.835 | 1.395 | 0.871 | 0.79 |
| *P*2 value | <0.001 | <0.001 | <0.001 | 0.004 | <0.001 | 0.045 | <0.001 | 0.07 | 0.167 | 2.803 | -2.717 |
| *t*3 value | 8.317 | 7.433 | 7.314 | 3.610 | 4.831 | 4.101 | 6.158 | 3.136 | 1.982 | 0.006 | 0.007 |
| *P*3 value | <0.001 | <0.001 | <0.001 | 0.001 | <0.001 | <0.001 | <0.001 | 0.002 | 0.051 | 4.037 | -3.882 |
| *t*4 value | 2.877 | 2.052 | 2.106 | 1.338 | 1.940 | 2.037 | 1.745 | 1.96 | 1.163 | <0.001 | <0.001 |
| *P*4 value | 0.005 | 0.043 | 0.038 | 0.185 | 0.056 | 0.045 | 0.085 | 0.053 | 0.248 | 2.110 | -2.029 |

Note: *t*1 value, *P*1 value: Differences in biochemical parameters between control and treatment group before treatment. *t*2 value, *P*2 value: Differences in biochemical parameters in control group before and after treatment. *t*3 value, *P*3 value: Differences in biochemical parameters in treatment group before and after treatment. *t*4 value, *P*4 value: Differences in biochemical parameters between control and treatment group after treatment.

**Table 2.** Comparison of treatment efficacy between two groups after treatment (n = 42)

| Group | Markedly effective (n) | Effective (n) | Ineffective (n) | Total effective rate (n/%) | $X^2$ value | *P value* |
|---|---|---|---|---|---|---|
| Control group | 3 | 26 | 13 | 29 (60.0) | | |
| Treatment groups | 15 | 23 | 4 | 38 (90.5) | 5.974 | 0.015 |

considered as the grade of liver steatosis in patients decreased by two grades (severe to mild or moderate to normal), effective was considered as the grade of liver steatosis in patients decreased by one grades. Ineffective was that the grade of liver steatosis was not changed, or liver steatosis was aggravated in patients. Total effective rate = (number of markedly effective + number of effective)/total number of cases × 100%.

*Statistical analysis*

SPSS 19.0 software (IBM SPSS, Armonk, NY, USA) was used for statistical analysis. Measurement data are expressed as the mean ± standard deviation. Differences between groups were compared using t-test (normal distribution) and Mann-Whitney U test (non-normal distribution). Enumeration data between groups were compared by Chi-square test. P<0.05 was considered to indicate a statistically significant difference.

## Results

*Changes in biochemical parameters in patients with NAFLD between two groups before and after treatment*

Before treatment, there was no statistical difference in biochemical parameters between the control and treatment groups. Compared with before treatment, the BMI, HbA1c, FPG, FIN, HOMA-IR, TG, TC, ALT, hs-CRP were significantly decreased in the control and treatment groups after 24-week treatment ($P$<0.05, $P$< 0.01). Compared with the control group, BMI, HbA1c, FPG, TG, and hs-CRP were significantly decreased in the treatment group ($P$<0.05, $P$<0.01). Although there was no statistically significant difference t in HOMA-IR, TC, and ALT between the two groups, but the HOMA-IR, TC, ALT had a decreasing trend in treatment group (**Table 1**).

*Treatment efficacy evaluated by abdominal Doppler ultrasound*

As shown in **Table 2**, after 24-week treatment, the total effective rate of treatment group (90.5%) was higher than the control group (69.0%).

*Adverse effects*

During the treatment, 3 patients in the control group developed gastrointestinal adverse events, including mild nausea and abdominal pain, whereas 2 patients in the treatment group had short-lasting mild diarrhea and abdominal distention. All side-effects were tolerable. Adverse events were not occurred after continuing treatment.

## Discussion

Prediabetes and NAFLD are both common chronic metabolic diseases that often coexist. There is a strong relationship between Prediabetes and n NAFLD [3, 6]. NAFLD has been recognized as a risk factor of diabetes. Patients with prediabetes complicated by NAFLD had severe abnormalities in the glucose metabolism, abnormal glucose metabolism not only significantly increases the risk of NAFLD, but also causes more serious hepatic lesions in NAFLD patients.

Hawthorn is a dried ripe fruit of Crataegus pinnatifida Bge. var. major N.E.Br. (Rosaceae family), which has been used in Chinese medicine for more than 2,000 years. Hawthorn was used to lower high blood pressure, reduce blood lipids, increase coronary blood flow, treat arrhythmias, enhance myocardial contractility, inhibit bacterial growth, improve digestive function, and invigorate the circulation of blood [7].

Metformin had no significant effect on liver histology in patients with NAFLD, so metformin is not currently recommended as a first-line treatment for NAFLD. However, metformin has an advantage in reducing insulin resistance and controlling body weight [8, 9]. So, hawthorn combined with metformin maybe an effective treatment for patients with prediabetes complicated by NAFLD.

In the present study, we investigated the effect of hawthorn combined with metformin in treat-

ing patients with prediabetes and NAFLD, the results show that compared with metformin administered alone, hawthorn combined with metformin significantly reduced body mass index, decreased HbA1c, FPG, 2hPG, and TG, and an increased tendency of insulin sensitivity, a decreased tendency of TC and ALT was observed. Treatment efficacy evaluated by abdominal Doppler ultrasound showed that hawthorn combined with metformin was superior to metformin administered alone in improving the hepatic architecture in patients with prediabetes complicated by NAFLD.

Oxidant stress and endoplasmic reticulum stress are major contributing factors to the pathogenesis of NAFLD [10], that lead to hepatocellular injury and inflammation. hs-CRP serves as an early marker of inflammation, plays an important role in the pathogenesis of NAFLD. Increased expression of serum hs-CRP is an independent risk factor for the development of NAFLD. In this study, we found that compared with metformin administered alone, hawthorn combined with metformin significantly reduced the hs-CRP expression. In our pervious animal study, we found that hawthorn can significantly reduce MDA content and significantly increase activities of serum superoxide dismutase (SOD), glutathione peroxidase (GSH-PX) activity of rat NAFLD model, indicating that hawthorn had favorable antioxidant effects [11]. Our results are consistent with the previous study [4].

In conclusion, combination treatment with hawthorn and metformin can reduce body weight, inhibit hs-CRP expression, reduce liver enzyme levels and the degree of liver steatosis, and improve NAFLD and prevent prediabetes. Also, combination treatment with hawthorn and metformin has very good safety and compliance which is an effective treatment for patients with prediabetes complicated by NAFLD. In the future, large controlled studies are needed to validate the present study results.

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## Disclosure of conflict of interest

None.

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