

**Commentary**

# Research Progress of Metformin in the Treatment of Non-alcoholic Fatty Liver Disease

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**Abstract:** *Background:* Nonalcoholic fatty liver disease has become the second largest source of chronic liver disease in the urban population. Metformin, a traditional drug, has good prospects for treating the disease in primary health care facilities. *Objective:* To summarize and grasp the status of metformin in adults, children with diabetes and non-diabetic NAFLD patients. *Methods:* We reviewed 31 relevant research literatures in PubMed database, and sorted out some preclinical and clinical research results. *Results:* Metformin was found to have a good effect in improving liver function indicators in both adult diabetic and non-diabetic NAFLD patients, and could benefit liver histology in NAFLD patients with adult diabetes. Metformin treatment did not show a significant advantage over lifestyle interventions in children with NAFLD. *Conclusion:* Metformin can improve the liver function and histological structure of adult NAFLD patients to a certain extent, and children patients should still be treated mainly with improved lifestyle.

**Keywords:** Non-alcoholic Fatty Liver Disease, Metformin, Diabetes

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## 1. Introduction

The nonalcoholic fatty liver disease (Non-alcoholic fatty liver disease, NAFLD) showed a trend of growing worldwide, has become a common after HBV chronic liver disease. The prevalence is between 20% and 46% in developed countries in Europe and the Americas [1]. The prevalence of nonalcoholic fatty liver disease in developing countries represented by China in Asia is between 5% and 40% [2]. The prevalence is highest in people aged 40 to 49 years [3]. This is the main cause of chronic liver disease in obese children [4].

The routine management of NAFLD will be left to a wide range of primary health-care institutions. NAFLD can be classified into non-alcoholic fatty liver (NAFLD) or non-alcoholic steatohepatitis (NASH) at two different clinical stages according to different pathological changes [5]. Some patients are concurrent with type 2 diabetes. Liver failure, cirrhosis, and hepatocellular carcinoma are the terminal

adverse outcomes of NASH [6]. Standardized drug intervention in early primary medical institutions plays a key role in stopping the occurrence of adverse outcomes. However, access to drugs and limited medical economy are the difficulties for primary medical institutions to carry out diagnosis and treatment. Therefore, the study on the pharmacological mechanism of traditional drugs in improving the prognosis of NAFLD is the focus of attention of doctors at the grassroots level.

The pathogenesis of NAFLD is not fully understood, and the pathophysiological "double strike" hypothesis has been gradually proposed: the "first strike" is the synergistic effect of obesity and diet, and the "second strike" is the mechanism of inflammation and cell damage. Insulin resistance is known to play a key role in the development of disease, and the "second strike" is an important reason for aggravating insulin resistance [7, 8]. Insulin resistance activates adipogenic transcription factor steroregulatory factor binding protein-1 (srebp-1) through the AMPK pathway to promote liver

adipogenesis, while peripheral adipolysis leads to increased flow of free fatty acids into the liver, leading to pathological changes in liver cell structure [9, 10]. In addition to adjusting diet and lifestyle, metformin is an insulin sensitizer that has been shown to improve insulin resistance and is a first-line oral therapy recommended by global guidelines for the treatment of type 2 diabetes mellitus (T2DM) [11, 12], which is readily available at all levels of medical centers. Multiple studies have confirmed the beneficial effects of metformin on the biochemical or histological characteristics of non-alcoholic fatty liver disease [13-16]. Metformin has also been shown to regulate the synthesis of tumor necrosis factor and interleukin-6 to increase  $\alpha$ -oxidation of free fatty acids and reduce *de novo* synthesis to prevent fat accumulation in the liver [9, 10, 17].

As a result, metformin has been widely recommended in several guidelines for the treatment of adult NAFLD with type 2 diabetes. However, will the drug benefit from its use in non-diabetic patients and at different ages, especially in children with NAFLD? Can metformin improve NASH organizational change? How is the dose of metformin controlled in the course of different diseases? It is still a difficult problem that needs urgent attention in clinical practice. Therefore, the purpose of this review is to summarize adult and pediatric studies, and to classify clinical studies of metformin in diabetic and non-diabetic NAFLD patients, including the results of liver biopsy after treatment, so as to provide more detailed basic data for the promotion and application of metformin in primary clinical NAFLD treatment.

## 2. Preclinical Study

Early evidence of metformin's benefit in the treatment of NAFLD came from preclinical studies in insulin-resistant mice with nonalcoholic fatty liver disease [13, 18]. Lin and H. Z et al found for the first time in mouse model that metformin improved fatty liver disease, reversed hepatocellular pathological changes, and normalized ALT levels, indicating that metformin could not only prevent and reverse the development of steatosis, but also prevent and reverse liver inflammation [13, 18]. Although metformin has shown significant therapeutic effects in mice with NAFLD, more clinical studies are needed to further validate it.

## 3. Clinical Study

### 3.1. Adult Diabetes

Because T2DM and nonalcoholic fatty liver share similar pathogenesis, T2DM appears as an important complication in many cases of nonalcoholic fatty liver disease. Metformin has sufficient indications for the treatment of T2DM, but whether NASH patients combined with T2DM can further obtain liver benefits and how the dose-response relationship is an issue to be discussed in clinical studies.

A small dose of metformin (1g/d) for half a year compared

with diet showed that both of them could improve liver metabolic parameters, confirming the priority of improving diet structure and living habits. However, small dose of metformin could improve liver function more significantly. In addition, liver steatosis was significantly improved in both groups [19]. Similar results were shown in another clinical trial with a low dose of metformin (850-1000 mg/d) [20]. These two studies suggest that a small dose of metformin can benefit liver function. However, a study that increased the dose of metformin to 2000 mg/day showed that only 30% of patients experienced histological reactions and improvements in alanine aminotransferase levels, which were associated with weight loss [21]. This suggests that increasing the dose of metformin does not necessarily lead to greater benefits. In addition, a 19-person randomized, placebo-controlled diet, exercise, and metformin diet and exercise trial showed no improvement in histology or liver enzyme levels in either group [22].

Omer et al [22] of 64 patients receiving metformin, combination treatment with rosiglitazone single-agent or both studies, the results show that metformin group is the only beneficial effects of body mass index falls significantly without changing the liver fat content and ALT levels increase hepatic insulin sensitivity, and the results of another study [23]. Nair et al [24] conducted post-treatment biopsies on 10 participants, after 3 months of treatment, insulin resistance improved, corresponding to a decrease in the levels of ALT and AST. However, during the study, insulin sensitivity was stable and transaminase increased gradually again. The histological changes were very slight. Loomba et al [21] studied the efficacy of metformin in NASH patients for 48 weeks, and the results showed that patients could obtain a corresponding tissue response with weight loss, and reduce hepatocyte injury and periental inflammation accordingly. Bugianesi et al [25] studied 110 patients with nonalcoholic fatty liver disease who were randomly given metformin or a control group (vitamin E or diet) for 12 months. ALT levels were significantly reduced in metformin patients, and follow-up biopsies of 17 patients showed improvements in steatosis, necroinflammation, fibrosis, and NASH index. Interestingly, a recent large case-control study showed that the use of metformin was dose-dependent with the reduction of HCC risk in diabetic patients [26]. The authors found a 7% reduction in HCC risk for each additional year of use. These results suggest that metformin in patients with nonalcoholic fatty liver disease may have a beneficial effect of ideal, small doses of metformin (800-1000 mg), liver function can obtain benefit, most studies support metformin treatment for NASH reversible hepatocyte steatosis, overall improve the histological structure, reduce inflammation and reduce NASH to the risk of HCC, liver failure and liver cirrhosis transformation.

### 3.2. Non-diabetic

Although current guidelines and the above studies support the recommendation of metformin for the treatment of nonalcoholic fatty liver disease with T2DM. However,

whether patients with nonalcoholic fatty liver disease without T2DM can benefit from it is a key issue we need to discuss. Uygun et al. [24] randomly selected 36 of T2DM patients with NASH, respectively treated with diet or diet plus metformin alone for six months, the results showed that the BMI of join the metformin group, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and insulin resistance index were improved significantly, necrotizing inflammation activity declined slightly, but the results did not reach statistical significance. Idilman et al. also demonstrated in a study of 74 NASH patients that diet plus metformin resulted in significant weight loss, reduced Alt, and insulin resistance, but no histological improvement. These studies suggest that metformin treatment of nonalcoholic fatty liver disease without T2DM can also reduce liver inflammatory markers and insulin resistance, but does not show significant histologic benefit in this group of patients. More evidence is needed to support the effect of metformin on liver histology in non-diabetic patients [8].

### 3.3. In Children

The paradoxes of the above studies point to the low dose of metformin used and the lack of significant improvement in insulin sensitivity may be the key reasons for the poor histologic changes. Although metformin has been shown to be effective in adult studies, it has shown different results in children. Two pediatric trials have been conducted [29, 30]. Nobili et al. evaluated the effect of diet plus metformin on nonalcoholic fatty liver disease in children aged 9-18 years for 2 years and found that metformin did not appear to be more effective than lifestyle interventions in improving transaminase levels, steatosis, and liver histology in children with NAFLD. Second study is by far the largest pediatric research, evaluated the 173 ages 8 to 17 patients with nonalcoholic fatty liver disease, they accepted the 96 weeks of vitamin E, metformin, or placebo, no a set of ALT levels continued to decline, the study has not been reported in the use of metformin in children with diabetes, any significant adverse events. These studies suggest that the focus of treatment for childhood NAFLD is still to improve lifestyle and adjust diet.

## 4. Conclusion

The proportion of patients with non-alcoholic fatty liver disease shows a trend of continuous growth with economic development, especially in economically developed urban and rural areas, and is also the most common cause of chronic liver disease in children and adolescents. The diagnosis and treatment of NAFLD will be left to the majority of primary medical institutions. Liver failure, cirrhosis, and hepatocellular carcinoma are the terminal adverse outcomes of NAFLD [6]. Standardized and effective drug intervention therapy in early primary medical institutions plays a key role in ending the occurrence of adverse outcomes. Understanding the pharmacological mechanism of traditional drugs in improving the prognosis of

NAFLD is the focus of grassroots doctors.

This review classifies and sorts out the relevant clinical research data in the early stage, and compares the research results of patients with and without diabetes, adults and children. It was concluded that metformin in the treatment of nonalcoholic fatty liver disease, higher dose may be more likely to cause weight loss, reduce insulin resistance, and thus improve liver histology [27-28]. Two studies using higher doses of metformin did find significant weight loss [20-21]. The dose of metformin was 2.5-3 g/day, with an average weight loss of 4 kg in 6 months, while the dose of metformin was 2 g/day, with an average weight loss of 6 kg in 1 year [20-21]. Only mild gi side effects were reported in all the studies, and only two had a patient drop out because the side effects were intolerable [20]. No cases of lactic acidosis were detected, and treatment for adults and children was safe, but treatment for children was not superior to lifestyle interventions.

Although metformin is effective in treating adult NAFLD patients with diabetes, it is still insufficient to undermine the role of lifestyle intervention in treatment, especially for children.

Although there have been many studies on metformin treatment of nonalcoholic fatty liver disease, few have been able to break down the differences between patients of different age groups and specific groups, especially children and pregnant women. It is believed that more and more detailed stratified research data will guide the clinical practice in the future.

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