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Original Article

The curative effect of metformin and linagliptin in newly-diagnosed type 2 diabetes patients with non-alcoholic fatty liver disease

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Abstract: Objective: To explore the efficacy of metformin combined with linagliptin in newly-diagnosed type 2 diabetes (NDTD) patients with non-alcoholic fatty liver disease (NAFLD). Methods: A total of 60 NDTD patients with NAFLD were recruited as the study cohort and randomized into a study group (SG, n=30) and a control group (CG, n=30). The patients in the CG received metformin alone, and the patients in the SG were treated with metformin and linagliptin. The patients' blood sugar levels, insulin secretions, inflammatory cytokines, liver fibrosis and fatty liver indicators, and incidences of adverse reactions were compared between the two groups. Results: After the treatment, the FPG, 2hPG, HbAlc, HOMA-1R, TNF-α, and CRP levels in the SG were decreased compared with the CG (P<0.05), but the GLP-1 levels in the SG were higher than they were in the CG (P<0.05). The response rate to the fatty liver treatment in the SG was 96.67%, higher than the 80.00% rate seen in the CG (P<0.05). The proportion of liver fibrosis in the SG after the intervention was significantly lower than it was in the CG (P<0.05). There were no significant differences in the numbers of adverse reactions in the two groups. (P>0.05). Conclusion: Metformin combined with linagliptin has a good therapeutic effect in patients with NDTD and NAFLD, and the combination can significantly improve a patient's islet function and body inflammation levels and safely relieve fatty liver and liver fibrosis.

Keywords: Newly-diagnosed type 2 diabetes, non-alcoholic fatty liver disease, metformin, linagliptin, efficacy

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to excessive fat build-up in the liver without another clear cause such as alcohol consumption [1]. It is an acquired metabolic disease characterized by fat deposition in the liver and is closely associated with insulin resistance and genetic susceptibility [2]. It encompasses a spectrum of diagnoses ranging from simple fatty liver (SFL) to non-alcoholic steatohepatitis (NASH). In recent years, following the changes in people's diets and lifestyles, the incidence of NAFLD has been increasing worldwide. The data show that the prevalence of NAFLD in adults is about 10%-30% [3, 4].

Clinical studies have found that NAFLD not only causes cirrhosis and hepatocellular carcinoma, but it also extensively participates in the occurrence and development of type 2 diabetes and atherosclerosis. These diseases or factors are risk factors for NAFLD, and insulin resistance has been shown to be the basic feature of this metabolic syndrome [5]. Data show that the incidence of NAFLD in patients with type 2 diabetes is as high as 70%, which is 2-3 times higher than the rate seen in healthy adults. The relationship between NAFLD and type 2 diabetes is bidirectional. Diabetes promotes the progression of NAFL to NASH, while NAFLD is a risk factor for developing type 2 diabetes. Clinical practice guidelines and research indicate that exercise intervention is a crucial means to prevent the progress of fatty liver disease, but the operability and controllability of exercise intervention are low. In addition, hepatoprotective drugs not only increase patients' financial burdens, they may even induce the risk of adverse reactions [6, 7].

Dipeptidyl peptidase 4 inhibitor (DPP-4 inhibitor) is a type 2 diabetes treatment developed in recent years. Metformin is a DPP-4 inhibitor that can selectively inhibit the activity of the DPP-4 enzyme to increase patients' GLP-1 levels, thereby increasing insulin secretions and inhibiting the secretion of glucagon [8]. This has been verified in many animal experiments. In addition, some studies have revealed that DPP-4 inhibitors also have the effect of increasing the sensitivity of the peripheral tissues to insulin, promoting the proliferation of pancreatic β-cells, and effectively lowering blood glucose levels in patients with type 2 diabetes under the combined action of multiple mechanisms [9]. Linagliptin is a new type of DPP-4 inhibitor with strong selectivity often used in the treatment of type 2 diabetes that has been proven to have a significant hypoglycemic effect and high safety in clinical practice. This study aimed to analyze the effectiveness of metformin combined with linagliptin in patients with NDTD and NAFLD, with a view to providing clinical evidence for improving the clinical symptoms and prognosis of such patients.

Materials and methods

Baseline data

A total of 60 patients with NDTD and NAFLD admitted to our hospital from June 2018 to June 2019 were recruited as the study cohort and randomly divided into a study group (SG, n=30) and a control group (CG, n=30). The SG included 16 males and 14 females, with an average age of (53.19 ± 3.22) years and an average BMI of (22.39 ± 2.31) kg/m^2. The CG included 15 males and 15 females, with an average age of (53.21 ± 3.19) years and an average BMI of (22.41 ± 2.26) kg/m^2.

Inclusion criteria: (1) Patients >18 years old, (2) patients with a confirmed diagnosis of type 2 diabetes, (3) patients who had not previously taken DPP-4 inhibitors (ligagliptin, vildagliptin, *etc*.), (4) patients who had not taken antibiotics or microbiological preparations within 4 weeks, (5) and patients whose NAFLD was confirmed through liver ultrasound/CT/MR, changes in liver enzymes, *etc*. The patients were informed of the study and signed the informed consent forms. This study was approved by ethics committee of the General Hospital of the Yangtze River Shipping.

Exclusion criteria: (1) Patients with type 1 diabetes, GDM, diabetes combined with severe acute and chronic complications, (2) patients who also suffered from severe organ dysfunction diseases, tumors, autoimmune diseases, *etc*., (3) patients who also suffered from various stomach and intestinal diseases, (4) patients who were allergic to linagliptin or to other drugs in its class, (5) patients who also had a mental illness, and (6) patients who had poor compliance.

Withdrawal criteria: (1) Patients who died during the study, (2) patients who voluntarily requested to quit the study, (3) patients who were lost during the study.

Interventions

In addition to the conventional treatment (dietary control, appropriate exercise, *etc*.), the patients in the CG were given metformin hydrochloride tablets (Sino-US Shanghai Squibb Pharmaceutical Co., Ltd., 0.5 g/tablet, H200-23370) via 50 mg, q.D, for 12 months. The patients in the SG were also given linagliptin tablets in addition to the treatment administered to the CG (Boehringer Ingelheim Pharmaceuticals Inc, 5 mg/tablet, J20171087) via 5 mg/time, q.D, for 12 months.

Outcome measurement

Changes in the blood glucose indices: Blood samples from the two groups were collected before the intervention and at 6 and 12 months after the intervention. The FPG, 2hPG, and HbAlc levels were determined using an automatic biochemical analyzer.

Comparison of the islet function: The pancreatic islet function indicators, GLP-1 and HOMA-IR were evaluated before the intervention and at 6 and 12 months after the intervention. The GLP-1 levels were measured using the enzyme-linked immune adsorption method (ELISA, Hefei Laier Biological Technology Co., Ltd). The HOMA-IR levels were calculated using the formula (FPG × fasting insulin/22.5) [10].

Comparison of the inflammatory levels: Blood samples from the two groups were collected

Table 1. Comparison of the clinical data between the two groups (mean ± SD)/[n (%)]

Data		Study group (n=30)	Control group (n=30)	t/X^2	*P*
Gender	Male	16	15	0.067	0.796
	Female	14	15		
Age (year)		53.19 ± 3.22	53.21 ± 3.19	0.024	0.981
Education level	Illiterate	1	2	0.443	0.712
	Primary school	4	4		
	Junior high school	10	10		
	High school and above	15	14		
Marital status	Married	28	27	0.218	0.64
	Unmarried	2	3		
Monthly income (yuan)	<1000	5	3	0.554	0.511
	1000-3000	15	16		
	>3000	10	11		
Average BMI (kg/m^2)		22.39 ± 2.31	22.41 ± 2.26	0.034	0.973

before the intervention and at 6 and 12 months after the intervention to measure the patients' TNF-α and CRP levels. The TNF-α levels were measured using ELISA (Hefei Laier Biological Technology Co., Ltd). The CRP levels were measured using a fully-automatic biochemical analyzer.

Comparison of the liver fibrosis indices: The two groups' liver fibrosis indices were analyzed before the intervention and at 6 and 12 months after the intervention. The FIB-4 index was used to evaluate the degree of fibrosis as follows: FIB-4 = [age (years) × AST (IU/L)]/[PLT (× 109/L) × ALT(IU/L)]. The cut-off point was 1.30-2.67. Moderate >1.30; Severe >2.67 [11].

Analysis of the fatty liver levels before and after the intervention: Before and at 12 months after the intervention, the two groups' fatty liver levels were evaluated using the CT ratio of the liver and spleen. 0.7-1.0 indicated mild fatty liver disease, 0.5-0.7 indicated moderate fatty liver disease, and <0.5 indicated severe fatty liver disease. The evaluation criteria for treatment effect were as follows: marked effect is clinical remission or the disappearance of fatty liver disease, effective means that the fatty liver was improved by one grade or more, and invalid means no change in the fatty liver grade after the intervention. The response rate = (marked effect + effective)/total number of cases.

Comparison of incidences of adverse reactions: Adverse reactions such as diarrhea, nausea and vomiting, skin allergies, *etc*. during the treatment were compared between the two groups.

Statistical methods

SPSS 19.0 was used for the data analysis. Continuous variables were expressed as the mean ± standard deviation (mean ± SD) and were compared using paired T tests. The comparisons between groups were analyzed using single factor analyses of variance. The comparisons of rates (%) were performed using chi-square tests. T tests were used for the difference analyses of continuous variables. $P<0.05$ was considered statistically significant [12].

Results

Comparison of the baseline data

There were no statistically significant differences in the two groups' clinical data, such as gender, age, or course of the disease, *etc*. ($P>0.05$), so the two groups were comparable (**Table 1**).

Changes in the blood glucose indices

The FPG, 2hPG, and HbAlc levels exhibited no significant difference between the two groups before the intervention ($P>0.05$). With the extension of the intervention time, the above indicators were deceased in both groups ($P<0.05$), and they were significantly lower in

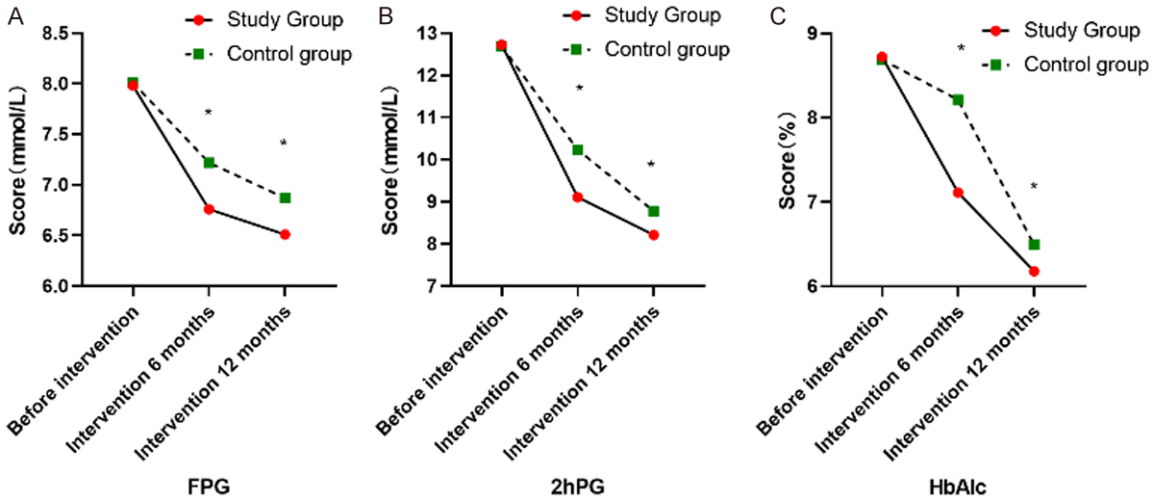

Figure 1. Comparison of the changes in the blood glucose indices between the two groups. There were no significant differences in the FPG, 2hPG, or HbAlc levels in the two groups before the intervention ($P>0.05$). At 6 and 12 months after the intervention, the FPG (A), 2hPG (B), and HbAlc (C) levels in the study group were significantly lower than they were in the control group ($P<0.05$). * compared with control group $P<0.05$.

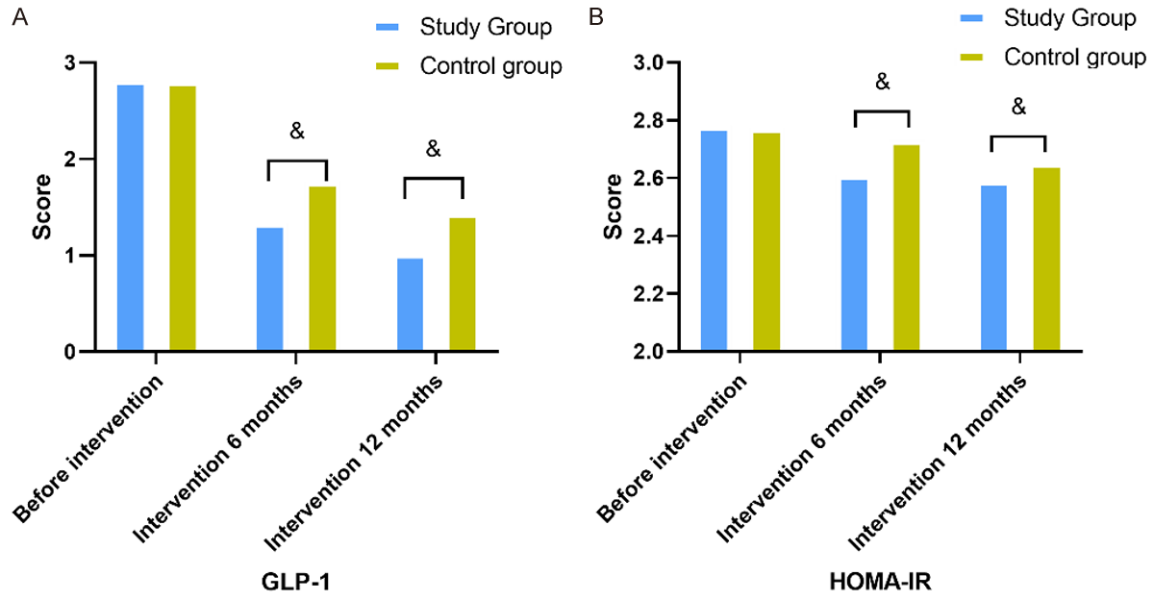

Figure 2. Comparison of islet function before and after intervention. There were no significant differences in the GLP-1 or HOMA-IR levels in the two groups before the intervention ($P>0.05$). At 6 and 12 months after the intervention, the GLP-1 (A) and HOMA-IR (B) levels in the study group were significantly lower than they were in the control group ($P<0.05$). & compared with the control group $P<0.05$.

the SG than they were in the CG ($P<0.05$) (**Figure 1**).

Comparison of the islet function

After the intervention, the two groups' GLP-1 and HOMA-IR levels showed a significant decrease ($P<0.05$), and they were lower in the SG than they were in the CG at 6 and 12 months after the intervention ($P<0.05$) (**Figure 2**).

Comparison of the inflammatory levels

There was no significant difference in the two groups' TNF-α and CRP levels before the intervention ($P>0.05$). After the intervention, the

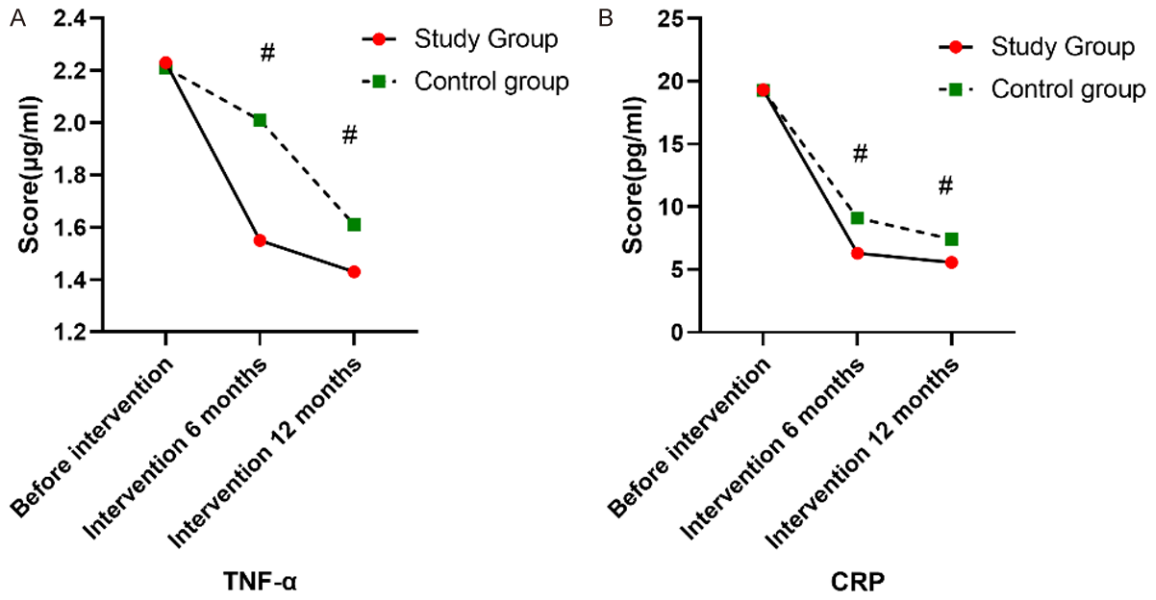

Figure 3. Comparison of the inflammatory index changes in the two groups. There was no significant difference in the TNF-α levels in the two groups before the intervention (P>0.05). After the intervention, the TNF-α levels in the two groups decreased significantly, and the level in the study group was lower than it was in the control group (P<0.05) (A). There was no significant difference in the CRP levels between the two groups before the intervention (P>0.05), and the CRP levels decreased significantly after the intervention. The CRP levels of the study group at 6 months and 12 months after the intervention were lower than they were in the control group (P<0.05). # compared with the control group (P<0.05) (B).

Table 2. Changes in the liver fibrosis indexes before and after the intervention in the two groups [n (%)]

	Group	Number of cases	Mild	Moderate	Severe
Before intervention	Study group	30	10 (33.33)	12 (40.00)	8 (26.67)
	Control group	30	11 (36.67)	12 (40.00)	7 (23.33)
	X^2	-	0.008	0.0	0.089
	P	-	0.931	1.0	0.766
After 30 days of intervention	Study group	30	19 (63.33)	11 (36.67)	0 (0.00)
	Control group	30	11 (36.67)	15 (50.00)	4 (13.33)
	X^2	-	4.267	1.086	4.286
	P	-	0.039	0.297	0.038

levels were significantly lower than they were before the treatment (P<0.05), and the TNF-α and CRP levels in the SG were lower than they were in the CG at 6 and 12 months after the intervention (P<0.05) (**Figure 3**).

Comparison of the liver fibrosis indices

The two groups showed no statistical differences in their proportions of mild, moderate, and severe liver fibrosis (P>0.05), but they showed significant differences after the intervention (P<0.05) (**Table 2**).

Analysis of fatty liver

The response rates were 96.67% in the SG and 80.00% in the CG. The two groups showed a significant difference in their fatty liver response rates (P<0.05) (**Table 3**).

Comparison of the incidences of adverse reactions

The two groups showed no significant difference in their incidences of adverse reactions (P>0.05) (**Table 4**).

Table 3. Comparison of the effectiveness of the fatty liver treatment [n (%)]

Group	Number of cases	Marked effect	Effective	Invalid	Response rate
Study group	30	20 (66.67)	9 (30.00)	1 (3.33)	29 (96.67)
Control group	30	15 (50.00)	9 (30.00)	6 (20.00)	24 (80.00)
X^2	-	-	-	-	4.043
P	-	-	-	-	0.044

Table 4. Comparison of the incidences of adverse reactions [n (%)]

Group	Number of cases	Nausea and vomit	Skin allergies	Diarrhea	Total incidence
Study group	30	2 (6.67)	2 (6.67)	1 (3.33)	5 (16.67)
Control group	30	1 (3.33)	2 (6.67)	1 (3.33)	4 (13.33)
X^2	-	-	-	-	0.131
P	-	-	-	-	0.718

Discussion

NAFLD is an umbrella term for a range of liver conditions that affect people who drink rarely or never drink alcohol. As the name implies, the main characteristic of NAFLD is excess fat stored in liver cells. This damage is similar to the damage caused by excessive drinking [13]. The incidence of NAFLD is rising linearly around the world. Epidemiological research data show that the prevalence of NAFLD in developed countries such as those in America and Europe is as high as 30%, but the prevalence of NAFLD in China is about 15% [14, 15]. The pathogenesis of NAFLD is explained as lipid metabolism disorders, insulin resistance, inflammation, and oxidative stress. In recent years, studies have also found that the occurrence and development of NAFLD are also related to the intestinal microenvironment (intestinal hormones and intestinal flora). Some NAFLD patients can develop nonalcoholic steatohepatitis (NASH), an aggressive form of fatty liver disease characterized by liver inflammation that may develop into advanced scarring (cirrhosis) and liver failure [16].

Researchers generally believe that NAFLD is linked to metabolic syndromes such as obesity, type 2 diabetes, hypertension, atherosclerosis, and triglyceride (TG) elevated dyslipidemia, which may be risk factors for NAFLD [17]. Insulin resistance is a central feature and "soil" of metabolic syndromes. We can infer that there is a large population of patients with diabetes and NAFLD [18]. The epidemiological data consistent with this theory suggest that the incidence of NAFLD in patients with type 2 diabetes is as high as 70%, which is 2-3 times higher than the incidence of NAFLD in adults. Diabetes is more difficult to manage when combined with NAFLD [19].

The clinical practice guidelines and expert consensus for NAFLD indicate that there is no effective treatment for simple fatty liver. Diet control and exercise are the most important and economical means to prevent the further development of NAFLD. It is found in clinical practice that lifestyle changes based on diet and exercise lack a certain degree of operability and controllability, so they may not effectively delay the progression of NAFLD [20]. If hepatoprotective drugs are used as routine treatment for simple fatty liver, not only have they not been recommended by the guidelines or recognized by the academic community, but they will also increase patients' financial burdens. There is no personalized treatment in the endocrine and hepatology field for NAFLD patients with diabetes. Diabetes drugs such as metformin, sulfonylureas, thiazolidinediones, insulin, DPP-4 inhibitors, and GLP-1 are still controversial in terms of their delaying the progress of NAFLD, so further research is needed to explore their efficacy and safety [21].

This study explored the effect of metformin combined with linagliptin in NDTD combined with NAFLD. The results showed that, compared with the CG, among the patients who were treated with metformin alone, the combination of linagliptin improved their blood glucose indices, suggesting that combination therapy can more effectively reduce patients' blood glucose levels. A survey of 80 patients with type 2 diabetes complicated with NAFLD showed that, compared with single-agent therapy, combination therapy is significantly better at improving the patients' clinical symptoms and regulating their blood glucose levels, and after 3 months of treatment, the blood glu-

cose levels of the patients who underwent combination therapy reached 97.50%, which was better than the 75.00% of the single-agent therapy [22]. The authors of this study believe that linagliptin is a DDP-4 inhibitor, and it can selectively act on DDP-4 enzyme activity and achieve the purpose of regulating blood glucose levels by raising patients' GLP-1 levels. The comparison of the islet function between the two groups of patients also confirmed this view. Studies have pointed out that GLP is a hormone secreted by intestinal epithelial cells that promotes insulin secretions and reduces the secretion levels of glucagon [23]. The results of this study showed that the combination of linagliptin and metformin also effectively reduced the patients' HOMA-IR levels, indicating that combination therapy can also help improve the sensitivity of the peripheral tissues to insulin This has also been demonstrated in other studies, so it can be concluded that linagliptin can improve the symptoms of hyperglycemia in patients with newly-diagnosed type 2 diabetes complicated with NAFLD by increasing their GLP-1 levels [24].

The study also analyzed the effect of two treatment methods on the inflammatory levels. The results showed that the combined treatment can effectively improve patients' inflammatory state and decrease their TNF-α and CRP levels. Animal experiments have revealed that hyperglycemia will result in enhanced lipid peroxidation in the liver. This process will lead to abnormally elevated inflammatory factor levels, such as serum TNF-α and CRP, which will further aggravate insulin resistance, and induce hepatic steatosis, necrosis, and fibrosis. This is also the main reason for the abnormal increase in liver fibrosis indicators in the two groups of patients before the treatment [25]. The results of the interventions in this study suggest that metformin combined with linagliptin improved the inflammatory state, liver fat metabolism, and fibrosis, which has been confirmed in many experiments. A study suggested that linagliptin can help improve the liver function of rats, and its long-term administration can alleviate liver fibrosis, which is similar to the results of this study [26]. Finally, we also found that the combined treatment did not significantly increase the incidence of adverse reactions in patients, suggesting that the treatment is safe.

In summary, the combined use of metformin and linagliptin has a good therapeutic effect on patients with NDTD and NAFLD, and it can significantly improve the patients' islet functions and inflammation, and help relieve fatty liver and liver fibrosis with high treatment safety. The shortcomings of this study are as follows: (1) The small sample size leads to a lack of comprehensiveness in the results obtained, and (2) The mechanism of combined treatment to improve liver fibrosis has not been thoroughly explored. We will next carry out a larger sample and more detailed research on the mechanism, in order to provide a theoretical basis for improving the clinical symptoms of patients with NDTD and NAFLD.

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Disclosure of conflict of interest

None.

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