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Effects of sitagliptin combined with dapagliflozin on liver function and glucose - lipid metabolism in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease

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Abstract: **Objective** To evaluate the clinical efficacy of sitagliptin combined with dapagliflozin in the treatment of type 2 diabetes mellitus (T2DM) complicated with non - alcoholic fatty liver disease (NAFLD), and to explore its multiple effects on liver function and glycolipid metabolism in patients. **Methods** From October 2022 to June 2024, 106 T2DM patients with NAFLD admitted to Jingzhou Third People''s Hospital were included as the study subjects. They were grouped complying with a random number table, with 53 patients in each group. The conventional group received oral treatment with dapagliflozin 10 mg per day, while the combination group received oral treatment with with dapagliflozin 10 mg per day plus sitagliptin 100 mg /d per day. Both groups continued treatment for 8 weeks for evaluation, and the changes in blood glucose, liver function, blood lipids, and insulin related indicators before and after treatment were compared between the two groups. **Results** After treatment, multiple biochemical indicators in both groups showed a great downward trend (P<0.05). Moreover, in the combined group, blood glucose control [fasting plasma glucose (FPG): (6.84±1.82) mmol/L *vs* (7.76±1.56) mmol/L, t=2.794, P=0.006] and lipid improvement [total cholesterol (TC): (4.58±0.73) mmol/L *vs* (4.94±0.86) mmol/L, t=2.323, P=0.022; low-density lipoprotein cholesterol (LDL-C): (2.75±0.86) mmol/L *vs* (3.19±0.97) mmol/L, t=2.471, P=0.015] and insulin resistance [insulin resistance index (HOMA-IR): In terms of (4.72±1.49) *vs* (5.45±1.63), t=2.406, P=0.018, both were significantly better than the conventional group, and the difference was statistically significant (P<0.05). **Conclusion** The combination therapy of sitagliptin and dapagliflozin has shown good therapeutic effects in T2DM patients with NAFLD. It can effectively improve glucose and lipid metabolism disorders and promote liver function recovery.

Keywords: Sitagliptin; Dapagliflozin; Type 2 diabetes mellitus; Liver function; Non-alcoholic fatty liver disease

In the medical field, type 2 diabetes mellitus (T2DM) is defined as a chronic disease characterized by gradual impairment of insulin function. The insulin produced by the body is insufficient to regulate blood glucose levels, thereby triggering various complications [1]. Nonalcoholic fatty liver disease (NAFLD) refers to the abnormal accumulation of fat within hepatocytes under the influence of non-alcoholic factors. Particularly, obese individuals are regarded as a high-risk group for this disease, a feature that shares certain similarities with T2DM [2]. NAFLD is currently the most prevalent type of chronic liver disease in clinical practice, thus posing a major global health challenge. It has a notably high incidence rate among the general population and T2DM patients, imposing a heavy disease burden [3].

Dapagliflozin is classified as a sodium-glucose cotransporter 2 (SGLT2) inhibitor. Its mechanism of action lies in inhibiting renal glucose reabsorption, promoting the excretion of more glucose through urine, and thereby achieving the goal of regulating blood glucose levels. Moreover, dapagliflozin does not depend on insulin secretion or action, making it equally effective for patients with insulin resistance [4]. However, long-term use may exert adverse effects on renal function. Sitagliptin belongs to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. It exhibits excellent lipid-regulating capabilities, can effectively reduce fat accumulation in patients, and significantly improve insulin resistance, with remarkable clinical application effects [5]. Based on these findings, this study aimed to analyze the effects of sitagliptin combined with dapagliflozin on liver function and glucose-lipid metabolism in T2DM patients complicated with NAFLD.

1 Materials and Methods

1.1 General Information

The sample size was calculated using the following formula: $n=\frac{\pi_1(100-\pi_1)+\pi_2(100-\pi_2)}{(\pi_1-\pi_2)^2}f(\alpha,\beta)$ In the formula, n represents the required sample size per group; π1 denotes the expected effective rate of the conventional treatment group (69.00%, based on preliminary pilot experiments); π2 is the expected effective rate of the combined treatment group (91.00%, based on preliminary pilot experiments); Type I error (α) = 0.05; Type II error (β) = 0.2. By querying relevant statistical tables, f(0.05,0.2)=7.9. Substituting the values into the formula, we obtained n=48. Considering a 10% dropout rate, at least 53 cases were required for each group.

A total of 106 T2DM patients complicated with NAFLD admitted to Jingzhou Third People's Hospital from October 2022 to June 2024 were selected as research subjects and equally divided into two groups using the random number table method, with 53 patients in each group. There were no statistically significant differences in baseline data such as gender, age, BMI, and duration of T2DM between the two groups (*P*>0.05), and no patients in either group had cirrhosis. See **Table 1.** This study was approved by the Medical Ethics Committee of Jingzhou Third People's Hospital (Approval No.: KYLL-2022063).

Tab.1 General information of the two groups（*n*=53）

Group	Male/Female (case)	Age (years)	BMI (kg/m²)	Duration of T2DM (years)
Combined group	29/24	60.48±9.67	27.04±5.68	8.15±3.22
Conventional group	27/26	60.32±10.05	27.08±4.71	8.47±3.58
χ^2/*t* value	0.151	0.089	0.039	0.484
***P* value**	0.697	0.929	0.969	0.630

1.2 Inclusion Criteria

(1)The diagnosis of T2DM patients must comply with the diagnostic criteria for T2DM specified in Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition) [6], with fasting plasma glucose (FPG) ≥ 7.0 mmol/L or 2-hour postprandial glucose (2hPG) ≥ 11.0 mmol/L; (2)NAFLD patients meet the diagnostic requirements for NAFLD in Guidelines for the Prevention and Treatment of Nonalcoholic Fatty Liver Disease (2018 Revised Edition) [7], and hepatic steatosis is confirmed by imaging examinations (e.g., B-ultrasound, CT, etc.); (3)Aged 18–75 years; (4)No history of epilepsy, dementia, or mental illness; (5)No significant allergic symptoms to the drugs used in this study and their related components; (6)The patient, their family members, or their guardians have signed the informed consent form.

1.3 Exclusion Criteria

(1)Patients with hyperthyroidism, anemia, or severe cardiac insufficiency; (2)Presence of drug-induced liver injury: acute or chronic liver injury caused by taking hepatotoxic drugs (such as glucocorticoids, methotrexate, sodium valproate, etc.); (3)Daily alcohol intake exceeding the threshold; (4)Patients with severe chronic gastrointestinal diseases or other digestive system diseases that affect drug absorption.

1.4 Dropout Criteria

(1)Loss to follow-up during the study period; (2)Patients who are not suitable for continuing treatment due to adverse events, complications, or special physiological changes; (3)Patients who voluntarily request to withdraw from the study.

1.5 Exclusion Criteria (for Data Analysis)

(1)Misdiagnosed cases or those who do not meet the inclusion criteria; (2)Patients with poor medication compliance (< 80%) after enrollment or failure to receive treatment according to the prescribed protocol, making it impossible to determine the therapeutic effect; (3)Patients who concurrently use other drugs affecting efficacy or safety during the study period.

1.6 Treatment Methods

Conventional group: Oral administration of dapagliflozin (National Medicine Approval No. HJ20170119, AstraZeneca Pharmaceuticals LP, specification: 10 mg/tablet), 1 tablet per day, taken in the morning without regard to meals.

Combined group: On the basis of conventional treatment, add sitagliptin phosphate (National Medicine Approval No. H20213477, Yangzijiang Pharmaceutical Group Guangzhou Hairui Pharmaceutical Co., Ltd., specification: 100 mg/tablet), 100 mg once daily, which can be taken with or without food.

Both groups received continuous treatment for 8 weeks to evaluate the therapeutic effect. Blood glucose monitoring was strengthened, and the treatment plan was gradually adjusted individually according to the evaluation results of the treatment response of patients in the two groups.

1.7 Observation Indicators

1.7.1 Glucose Metabolism Indicators

Before and after treatment, FPG and 2hPG of patients were measured by fingertip blood sampling using a blood glucose meter. Meanwhile, fasting venous blood samples were collected from patients before and after treatment, and the level of glycated hemoglobin (HbA1c) was determined using an HbA1c analyzer.

1.7.2 Blood Lipid and Liver Function Indicators

Fasting venous blood samples were collected from patients in both groups before and after treatment, and serum was separated for the detection of blood lipids and liver function. Serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels were determined using TC and HDL-C detection kits (based on enzymatic method); serum triglyceride (TG) content was measured using a TG detection kit (based on acetylacetone microplate method); serum low-density lipoprotein cholesterol (LDL-C) level was determined using an LDL-C detection kit (using polyethylene sulfate precipitation method). Serum liver function indicators such as alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GT), and aspartate aminotransferase (AST) were detected using an automatic biochemical analyzer.

1.7.3 Insulin-Related Indicators

Serum fasting insulin (FINS) level of patients was detected by radioimmunoassay, and the following indices were calculated: Homeostasis model assessment of insulin resistance index (HOMA-IR), calculated as (FINS×FPG)/22.5; Homeostasis model assessment of β-cell function index (HOMA-β), calculated as (20×FINS)/(FPG-3.5).

1.8 Statistical Methods

Data were processed using SPSS 24.0 software. Measurement data conforming to normal distribution were expressed as $\bar{x}\pm s$, and differences between groups were evaluated by independent samples *t*-test. A *P* value < 0.05 was considered statistically significant.

2 Results

2.1 Comparison of Glucose Metabolism Indicators between the Two Groups

Before treatment, there were no statistically significant differences in FPG, 2hPG, and HbA1c levels between the two groups (P>0.05). After 8 weeks of treatment, FPG, 2hPG, and HbA1c levels in both groups decreased significantly ($P<0.05$), and those in the combined group were significantly lower than those in the conventional group ($P<0.05$). See **Table 2**.

2.2 Comparison of Blood Lipid Indicators between the Two Groups

Before treatment, there were no statistically significant differences in HDL-C, TG, TC, and LDL-C levels between the two groups ($P>0.05$). After treatment, TG, LDL-C, and TC levels in both groups decreased ($P<0.05$), while HDL-C levels increased ($P<0.05$). After treatment, TG, TC, and LDL-C levels in the combined group were significantly lower than those in the conventional group ($P<0.05$), and HDL-C levels were significantly higher than those in the conventional group ($P<0.05$). See **Table 3**.

2.3 Analysis of Insulin-Related Indicators between the Two Groups

Before treatment, there were no statistically significant differences in HOMA-β and HOMA-IR levels between the two groups ($P>0.05$). After treatment, HOMA-IR levels in both groups decreased ($P<0.05$), while HOMA-β levels increased significantly ($P<0.05$). After treatment, HOMA-IR levels in the combined group were significantly lower than those in the conventional group ($P<0.05$), and HOMA-β levels were significantly higher than those in the conventional group ($P<0.05$). See **Table 4**.

2.4 Comparison of Liver Function Indicators between the Two Groups

Before treatment, there were no statistically significant differences in ALT, γ-GT, and AST levels between the two groups ($P>0.05$). After treatment, ALT, γ-GT, and AST levels in both groups decreased significantly ($P<0.05$), and those in the combined group were lower than those in the conventional group ($P<0.05$). See **Table 5**.

Tab.2 Comparison of FPG，2hPG and HbA1c levels between the two groups (n=53，$\bar{x}\pm s$)

Group	FPG（mmol/L）		2h PG（mmol/L）		HbA1c（%）	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined group	9.53±2.17	6.84±1.82[a]	14.34±3.78	8.42±2.53[a]	8.91±1.97	6.99±1.14[a]
Conventional group	9.33±2.11	7.76±1.56[a]	14.12±3.86	10.13±3.27[a]	8.94±1.82	7.64±1.39[a]
***t* value**	0.481	2.794	0.296	3.011	0.081	2.632
***P* value**	0.631	0.006	0.767	0.003	0.935	0.010

Tab.3 Comparison of HDL-C，TG，TC and LDL-C levels between the two groups （n=53，mmol/L，$\bar{x}\pm s$）

Group	LDL-C		TC		HDL-C		TG	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined group	3.67±1.19	2.75±0.86[a]	5.34±1.74	4.58±0.73[a]	1.09±0.35	1.35±0.41[a]	2.63±0.78	2.03±0.42[a]
Conventional group	3.53±1.12	3.19±0.97[a]	5.42±1.69	4.94±0.86[a]	1.07±0.33	1.18±0.37[a]	2.57±0.73	2.26±0.63[a]
***t* value**	0.624	2.471	0.240	2.323	0.303	2.241	0.409	2.211
***P* value**	0.534	0.015	0.811	0.022	0.763	0.027	0.683	0.029

Tab.4 Comparison of HOMA-IR and HOMA-β levels between the two groups （n=53，$\bar{x}\pm s$）

Group	HOMA-IR		HOMA-β	
	Before treatment	After treatment	Before treatment	After treatment
Combined group	6.90±2.11	4.72±1.49[a]	29.53±7.51	48.29±8.75[a]
Conventional group	6.87±2.09	5.45±1.63[a]	30.99±8.23	44.17±9.51[a]
***t* value**	0.074	2.406	0.954	2.321
***P* value**	0.942	0.018	0.342	0.022

Tab.5 Comparison of ALT，γ-GT and AST levels between the two groups （n=53，u/L，$\bar{x}\pm s$）

Group	ALT		γ-GT		AST	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined group	67.52±18.96	33.79±10.26[a]	123.20±20.43	63.45±12.31[a]	63.08±18.37	33.80±10.75[a]
Conventional group	67.69±17.52	40.61±12.53[a]	122.79±20.58	68.94±12.45[a]	63.66±19.22	39.84±11.08[a]
t value	0.048	3.066	0.103	2.283	0.159	2.848
P value	0.962	0.003	0.918	0.024	0.874	0.005

3 Discussion

T2DM is regarded as an extremely critical risk factor for cardiovascular diseases and is closely associated with the high incidence and severity of NAFLD. Numerous studies have explored the complex and interactive relationship between NAFLD and T2DM. Data show that more than half of T2DM patients are complicated with NAFLD [8]. NAFLD refers to the condition of abnormal lipid deposition in the liver in the absence of excessive alcohol consumption or exclusion of other known causes [9]. NAFLD is a liver disease whose pathogenesis is related to the combined effects of multiple factors, including genetic predisposition, insulin resistance, obesity, T2DM and other metabolic diseases, as well as environmental factors. Its pathogenesis involves ectopic accumulation of TG in the liver, especially due to increased free fatty acids produced by excessive hydrolysis of TG in adipose tissue, increased hepatic fatty acid synthesis caused by excessive carbohydrates, and contributions from chylomicrons and very low-density lipoproteins taken up from plasma. When an imbalance occurs between hepatic lipid storage and clearance rate, it will lead to hepatic steatosis, which may further develop into severe stages such as steatohepatitis and steatocirrhosis [10]. Although studies have shown that NAFLD can be effectively treated by adjusting diet and increasing exercise, current therapeutic interventions often fail to achieve long-term sustained effects in practical application [11].

Dapagliflozin can effectively block the process of renal glucose reabsorption, thereby preventing excessive accumulation of glucose in the body, helping to accurately regulate patients' blood glucose levels, and promoting the improvement of islet cell function [12]. Studies have shown that SGLT2 inhibitor therapy can effectively reduce liver fat content and thus improve liver function, and the degree of reduction in liver fat content is positively correlated with weight changes and improvement of HOMA-IR; for patients diagnosed with T2DM and NAFLD/nonalcoholic steatohepatitis, SGLT2 inhibitors may be the preferred treatment option [13]. Studies have shown that the level of DPP-4 is generally increased in T2DM patients complicated with NAFLD, indicating that it plays a key role in the pathogenesis of these diseases. Therefore, DPP-4 is regarded as a potential target for the treatment of T2DM complicated with NAFLD [14]. As a DPP-4 inhibitor, sitagliptin is recommended as the preferred alternative treatment drug for diabetes due to its excellent blood glucose regulating ability and good safety. This class of drugs exhibits protective effects on the cardiovascular system by optimizing insulin sensitivity and reducing inflammatory responses [15]. This study showed that the combined group treated with sitagliptin combined with dapagliflozin had a more significant effect in lowering blood glucose than dapagliflozin alone, which was consistent with previous research results [16]. Meanwhile, HOMA-IR levels decreased significantly, indicating that insulin resistance was improved; at the same time, HOMA-β levels increased significantly, suggesting that islet β-cell function was restored. In addition, the combined group showed better performance in improving HOMA-IR and increasing HOMA-β than the conventional group, which was consistent with relevant reports [17], further proving the superiority and comprehensive benefits of sitagliptin combined with dapagliflozin in the treatment of T2DM. However, there are few studies on the combined use of these two drugs in T2DM complicated with NAFLD. Meanwhile, dyslipidemia is one of the common pathological features of NAFLD and T2DM. In this study, TG, TC, and LDL-C levels of patients receiving combined treatment were significantly lower than those of the conventional group, while HDL-C levels were significantly higher than those of the conventional group, indicating that the combined use of SGLT2 inhibitors and DPP-4 inhibitors has significant advantages in regulating lipid metabolism in T2DM patients [18]. The normal content of ALT in blood is relatively low. When hepatocytes are damaged, ALT will be rapidly released from cells into the blood, resulting in a significant increase in blood ALT levels in a short time [19]. γ-GT is mainly derived from the liver. Obstruction of intrahepatic or extrahepatic bile ducts will lead to an increase in blood γ-GT concentration [20-21]. When hepatocytes are damaged and necrotic, AST originally present in the cytoplasm will be released into the blood, thereby causing a significant increase in serum AST levels [22]. After treatment, liver function indicators including AST, γ-GT, and ALT in both groups showed a significant downward trend, indicating that both treatment regimens had a positive effect on improving liver function, and the combined group was superior to the conventional group. Dapagliflozin has anti-inflammatory and antioxidant effects and can reduce liver inflammatory responses [23]; sitagliptin indirectly improves the liver microenvironment by regulating the GLP-1 signaling pathway [5]. Previous studies have confirmed that SGLT2 inhibitors and DPP-4 inhibitors respectively have hepatoprotective effects on NAFLD [24], but the effect of their combined treatment on liver function in NAFLD remains to be explored in clinical practice and mechanism research.

In conclusion, the combined application of sitagliptin and dapagliflozin has shown effectiveness in the treatment of T2DM complicated with NAFLD, exerting a synergistic effect through multiple mechanisms, including improving insulin resistance, regulating glucose-lipid metabolism, and reducing liver function damage. In future research, it is necessary to further explore the long-term safety and side effects of the combined therapy of sitagliptin and dapagliflozin; conduct further stratified analysis of NAFLD, not only limited to observing the effect of the combination of SGLT2 inhibitors and DPP-4 inhibitors on serum liver function indicators, but also exploring their effects on liver fat content and fibrosis, so as to obtain a more accurate and optimized treatment strategy for T2DM complicated with NAFLD.

Conflict of interest None

Reference

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·论　著·

西格列汀联合达格列净对2型糖尿病合并非酒精性脂肪肝患者肝功能、糖脂代谢的影响

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摘要：目的　评估西格列汀联合达格列净治疗2型糖尿病(T2DM)合并非酒精性脂肪肝病(NAFLD)的临床作用，并探讨其对患者肝功能与糖脂代谢的多重效应。**方法**　选取2022年10月至2024年6月荆州市第三人民医院接收的106例T2DM合并NAFLD且非肝硬化的患者作为研究对象，依照随机数字表划分成两组，每组53例。常规组口服达格列净10 mg/d；联合组口服达格列净10 mg/d+西格列汀100 mg/d。两组均持续治疗8周进行评价，对比两组患者糖代谢、肝功能、血脂和胰岛素相关指标水平在治疗前后的变化。**结果**　治疗后，两组患者的多项生化指标均呈现显著下降趋势($P<0.05$)，且与对照组比较，联合组在血糖控制[空腹血糖(FPG)：(6.84±1.82)mmol/L *vs* (7.76±1.56)mmol/L，$t=2.794$，$P=0.006$]、血脂改善[总胆固醇(TC)：(4.58±0.73)mmol/L *vs* (4.94±0.86)mmol/L，$t=2.323$，$P=0.022$；低密度脂蛋白胆固醇(LDL-C)：(2.75±0.86)mmol/L *vs* (3.19±0.97)mmol/L，$t=2.471$，$P=0.015$]及胰岛素抵抗方面[稳态模型评估的胰岛素抵抗指数(HOMA-IR)：4.72±1.49 *vs* 5.45±1.63，$t=2.406$，$P=0.018$]方面均显著优于常规组，差异有统计学意义。**结论**　西格列汀与达格列净联合治疗方案在T2DM合并NAFLD患者中展现出良好的治疗作用，能有效改善胰岛素抵抗，调节糖脂代谢紊乱，促进肝功能恢复。

关键词：西格列汀；达格列净；2型糖尿病；非酒精性脂肪性肝病；肝功能；胰岛素抵抗；糖代谢；脂代谢
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Effects of sitagliptin combined with dapagliflozin on liver function and glucose - lipid metabolism in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease

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Abstract: Objective　To evaluate the clinical efficacy of sitagliptin combined with dapagliflozin in the treatment of type 2 diabetes mellitus (T2DM) complicated with non-alcoholic fatty liver disease (NAFLD), and to explore its multiple effects on liver function and glycolipid metabolism in patients. **Methods**　From October 2022 to June 2024, 106 T2DM patients with NAFLD admitted to Jingzhou Third People's Hospital were included as the study subjects. They were grouped complying with a random number table, with 53 patients in each group. The conventional group received oral treatment with dapagliflozin 10 mg per day, while the combination group received oral treatment with dapagliflozin 10 mg per day plus sitagliptin 100 mg per day. Both groups continued treatment for 8 weeks for evaluation, and the changes in blood glucose, liver function, blood lipids, and insulin related indicators before and after treatment were compared between the two groups. **Results**　After treatment, multiple biochemical indicators in both groups showed a great downward trend ($P<0.05$). Moreover, in the combined group, blood glucose control [fasting plasma glucose (FPG): (6.84±1.82) mmol/L *vs* (7.76±1.56) mmol/L, $t=2.794$, $P=0.006$] and lipid improvement [total cholesterol (TC): (4.58±0.73) mmol/L *vs* (4.94±0.86) mmol/L, $t=2.323$, $P=0.022$; low-density lipoprotein cholesterol (LDL-C):

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(2.75±0.86) mmol/L *vs* (3.19±0.97) mmol/L, t=2.471, P=0.015] and insulin resistance [insulin resistance index (HOMA-IR): (4.72±1.49) *vs* (5.45±1.63), t=2.406, P=0.018], both were significantly better than the conventional group, and the difference was statistically significant (P<0.05). **Conclusion** The combination therapy of sitagliptin and dapagliflozin has shown good therapeutic effects in T2DM patients with NAFLD. It can effectively improve glucose and lipid metabolism disorders and promote liver function recovery.

Keywords: Sitagliptin; Dapagliflozin; Type 2 diabetes mellitus; Non alcoholic fatty liver disease; Liver function; Insulin resistance; Glycometabolism; Lipid metabolism

在医学领域,2型糖尿病(type 2 diabetes mellitus, T2DM)被定义为一种慢性疾病,患者胰岛素功能逐渐减弱,机体产生的胰岛素不足以调节血糖水平,进而引发各种并发症[1]。非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是在非酒精因素作用下,肝细胞内部脂肪异常积累的状态,尤其肥胖个体被视为该疾病的高发人群,这一特点与T2DM具有一定的相似性[2]。NAFLD是目前临床实践中最为普遍的慢性肝病类型,从而构成全球范围内的一个重大健康挑战,其在普通人群及T2DM患者中尤为高发,疾病负担沉重[3]。达格列净归类于钠-葡萄糖协同转运蛋白2(sodium-glucose cotransporter 2, SGLT2)抑制剂,其作用机制在于抑制肾脏对葡萄糖的重吸收,促使更多的葡萄糖通过尿液排出,进而达到调节血糖水平的目的,且达格列净不依赖于胰岛素的分泌或作用,因此对于胰岛素抵抗的患者同样有效[4]。但长期使用可能对肾脏功能产生不利影响。西格列汀属于二肽基肽酶-4(dipeptidyl peptidase-4, DPP-4)抑制剂,其展现出卓越的血脂调控能力,能够有效减少患者体内的脂肪积聚,并显著改善胰岛素抵抗状况,在临床实践中,西格列汀的应用效果显著[5]。基于此,本研究分析西格列汀联合达格列净治疗T2DM合并NAFLD,对患者肝功能、糖脂代谢的影响。

1 资料与方法

1.1 一般资料 样本量计算公式为:$n=\dfrac{\pi_1(100-\pi_1)+\pi_2(100-\pi_2)}{(\pi_1-\pi_2)^2}f(\alpha,\ \beta)$,上式中,$n$为每组所需样本量,$\pi_1$为常规组预期有效率(69.00%,基于前期预实验),π_2为联合组预期有效率(91.00%,基于前期预实验),Ⅰ类错误(α)=0.05,Ⅱ类错误(β)=0.2,查得f(0.05, 0.2)=7.9。代入计算得n=48,考虑10%脱落率后每组至少需53例。

选取2022年10月至2024年6月荆州市第三人民医院接收的106例T2DM合并NAFLD患者作为研究对象,通过随机数字表法平均分为两组,每组各53例。两组性别、年龄、身体质量指数(body mass index, BMI)、T2DM病程比较差异无统计学意义(P>0.05),且两组患者均未出现肝硬化。见表1。本研究获荆州市第三人民医院医学伦理委员会审批通过(批号:KYLL-2022063)。

表1 两组一般资料 (n=53)

Tab.1 General information of the two groups (n=53)

组别	性别(例)		年龄	BMI	T2DM病程
	男	女	(岁, $\bar{x}\pm s$)	(kg/m², $\bar{x}\pm s$)	(年, $\bar{x}\pm s$)
联合组	29	24	60.48±9.67	27.04±5.68	8.15±3.22
常规组	27	26	60.32±10.05	27.08±4.71	8.47±3.58
χ^2/t值	0.151		0.089	0.039	0.484
P值	0.697		0.929	0.969	0.630

1.2 纳入标准 (1) T2DM患者的诊断需遵循《中国2型糖尿病防治指南(2020年版)》[6]中T2DM的诊断标准,其中空腹血糖(fasting plasma glucose, FPG)≥7.0 mmol/L,或餐后2 h血糖(2-hour postprandial glucose, 2hPG)≥11.1 nmol/L;(2) NAFLD患者满足《非酒精性脂肪性肝病防治指南(2018年更新版)》[7]中NAFLD的诊断要求,且影像学检查(例如B超、CT等)确认存在肝脏脂肪变性;(3) 年龄18~75岁;(4) 非癫痫发作者、未患有痴呆或精神疾病;(5) 对本研究药物及相关成分均无显著过敏症状;(6) 患者或其家属或其监护人签署知情同意书。

1.3 排除标准 (1) 甲亢、贫血、严重心功能不全者;(2) 存在药物性肝损伤,即服用损伤肝脏的药物(如糖皮质激素、甲氨蝶呤、丙戊酸钠等)所致急慢性肝损伤;(3) 每日酒精摄入量超过阈值者;(4) 严重慢性胃肠道疾病者或其他消化系统疾病,影响药物吸收者。

1.4 脱落标准 (1) 研究期间失访者;(2) 因发生不良事件、并发症或特殊生理变化,不宜继续接受治疗者;(3)患者自行要求退出研究。

1.5 剔除标准 (1) 误诊或不符合纳入标准者;(2) 入组后用药依从性差(<80%)或未按规定方案治疗,无法判定疗效者;(3) 研究期间同时使用其他影响疗效或安全性的药物者。

1.6 治疗方法 常规组:口服达格列净(国药准字HJ20170119, AstraZeneca Pharmaceuticals LP,规格:

10 mg/片),每日仅需服用1片,于早晨服用,且无需考虑饮食因素。联合组:在常规治疗的基础上加用磷酸西格列汀(国药准字H20213477,扬子江药业集团广州海瑞药业,规格:100 mg/片),每日口服1次,100 mg/次,本品可与或不与食物同服。两组均持续治疗8周评价疗效,加强血糖监测,根据两组患者治疗反应的评估结果再逐渐个体化地调整治疗方案。

1.7 观察指标

1.7.1 糖代谢指标 在治疗前后,通过指尖采血并使用血糖仪来测量患者的FPG和2hPG。同时,在治疗前后采集患者空腹时的静脉血样,利用糖化血红蛋白(glycated hemoglobin,HbA1c)分析仪进行HbA1c水平的测定。

1.7.2 血脂和肝功能指标 在空腹状态下,分别于治疗前后从两组患者的静脉中采集血样,分离血清,用于血脂和肝功能检测。采用总胆固醇(total cholesterol, TC)和高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)检测试剂盒(基于酶法)测定血清中的TC及HDL-C水平;三酰甘油(triglyceride, TG)检测试剂盒(基于乙酰丙酮微板法)检测血清中的TG含量;低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)检测试剂盒(使用聚乙烯硫酸沉淀法)测定血清中LDL-C水平。采用全自动生化仪检测血清丙氨酸氨基转移酶(alanine aminotransferase, ALT)、谷氨酰转肽酶(γ-glutamyl transpeptidase, γ-GT)、门冬氨酸氨基转移酶(aspartate aminotransferase, AST)等肝功能指标。

1.7.3 胰岛素相关指标 放射免疫法检测患者血清空腹胰岛素(fasting Insulin, FINS)水平,并计算以下指数:稳态模型评估的胰岛素抵抗指数(insulin resistance index of homeostasis model assessment, HOMA-IR),其计算公式为(FINS×FPG)/22.5;稳态模型评估的胰岛β细胞功能指数(homeostatic model assessment of β-cell function, HOMA-β),计算公式为(20×FINS)/(FPG−3.5)。

1.8 统计学方法 利用SPSS 24.0软件对数据进行分析。符合正态性的计量资料采用$\bar{x}\pm s$形式进行表述,通过独立样本t检验评估不同组间差异。$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组糖代谢指标水平比较 治疗前,两组患者的FPG、2hPG、HbA1c水平相比差异无统计学意义($P>0.05$)。经8周治疗后,两组患者的FPG、2hPG、HbA1c均出现显著下降($P<0.05$),且联合组显著低于常规组($P<0.05$)。见表2。

2.2 两组血脂指标水平 在治疗前,两组患者的HDL-C、TG、TC以及LDL-C水平相比,差异无统计学意义($P>0.05$)。经过治疗,两组患者的TG、LDL-C、TC水平均下降($P<0.05$),而HDL-C水平则上升($P<0.05$)。联合组患者在治疗后,其TG、TC、LDL-C水平均显著低于常规组($P<0.05$),同时HDL-C水平显著高于常规组($P<0.05$)。见表3。

2.3 两组胰岛素相关水平分析 治疗前两组患者的HOMA-β和HOMA-IR水平差异无统计学意义($P>0.05$)。经过治疗,两组患者的HOMA-IR水平均下降

表2 两组患者FPG、2hPG、HbA1c水平比较 (n=53, $\bar{x}\pm s$)

Tab.2 Comparison of FPG, 2hPG and HbA1c levels between the two groups (n=53, $\bar{x}\pm s$)

组别	FPG(mmol/L)		2hPG(mmol/L)		HbA1c(%)	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
联合组	9.53±2.17	6.84±1.82[a]	14.34±3.78	8.42±2.53[a]	8.91±1.97	6.99±1.14[a]
常规组	9.33±2.11	7.76±1.56[a]	14.12±3.86	10.13±3.27[a]	8.94±1.82	7.64±1.39[a]
t值	0.481	2.794	0.296	3.011	0.081	2.632
P值	0.631	0.006	0.767	0.003	0.935	0.010

注:与同组治疗前比较,[a]$P<0.05$。

表3 两组患者HDL-C、TG、TC、LDL-C水平比较 (n=53, mmol/L, $\bar{x}\pm s$)

Tab.3 Comparison of HDL-C, TG, TC and LDL-C levels between the two groups (n=53, mmol/L, $\bar{x}\pm s$)

组别	LDL-C		TC		HDL-C		TG	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
联合组	3.67±1.19	2.75±0.86[a]	5.34±1.74	4.58±0.73[a]	1.09±0.35	1.35±0.41[a]	2.63±0.78	2.03±0.42[a]
常规组	3.53±1.12	3.19±0.97[a]	5.42±1.69	4.94±0.86[a]	1.07±0.33	1.18±0.37[a]	2.57±0.73	2.26±0.63[a]
t值	0.624	2.471	0.240	2.323	0.303	2.241	0.409	2.211
P值	0.534	0.015	0.811	0.022	0.763	0.027	0.683	0.029

注:与同组治疗前比较,[a]$P<0.05$。

(P<0.05)，而HOMA-β水平则显著上升(P<0.05)，且治疗后联合组的HOMA-IR水平显著低于常规组(P<0.05)，HOMA-β水平显著高于常规组(P<0.05)。见表4。

2.4 两组肝功能水平比较 治疗前，两组患者ALT、γ-GT、AST水平差异无统计学意义(P>0.05)；治疗后，两组患者ALT、γ-GT、AST水平均显著下降(P<0.05)，且联合组水平相较于常规组更低(P<0.05)。见表5。

表4 两组患者HOMA-IR、HOMA-β水平比较 (n=53, $\bar{x}\pm s$)

Tab.4 Comparison of HOMA-IR and HOMA-β levels between the two groups (n=53, $\bar{x}\pm s$)

组别	HOMA-IR		HOMA-β	
	治疗前	治疗后	治疗前	治疗后
联合组	6.90±2.11	4.72±1.49[a]	29.53±7.51	48.29±8.75[a]
常规组	6.87±2.09	5.45±1.63[a]	30.99±8.23	44.17±9.51[a]
t值	0.074	2.406	0.954	2.321
P值	0.942	0.018	0.342	0.022

注：与同组治疗前比较，[a]P<0.05。

表5 两组患者ALT、γ-GT、AST水平比较 (n=53, u/L, $\bar{x}\pm s$)

Tab.5 Comparison of ALT, γ-GT and AST levels between the two groups (n=53, u/L, $\bar{x}\pm s$)

组别	ALT		γ-GT		AST	
	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
联合组	67.52±18.96	33.79±10.26[a]	123.20±20.43	63.45±12.31[a]	63.08±18.37	33.80±10.75[a]
常规组	67.69±17.52	40.61±12.53[a]	122.79±20.58	68.94±12.45[a]	63.66±19.22	39.84±11.08[a]
t值	0.048	3.066	0.103	2.283	0.159	2.848
P值	0.962	0.003	0.918	0.024	0.874	0.005

注：与同组治疗前比较，[a]P<0.05。

3 讨论

T2DM被视为心血管疾病的一个极为关键的风险因素，并且与NAFLD的高发病率及其严重程度有着紧密的关联。众多研究深入探讨NAFLD与T2DM之间复杂且相互影响的联系，有数据显示在T2DM患者中，约有半数以上的患者同时伴有NAFLD[8]。NAFLD是指在没有过量饮酒或排除其他已知原因的情况下，肝脏内出现异常脂质沉积的状况[9]。NAFLD是一种肝脏疾病，其发病与多种因素相关，包括遗传倾向、胰岛素抵抗、肥胖、T2DM等代谢性疾病，以及环境因素等共同作用，其发病机制涉及TG在肝脏中的异位积累，特别是由于脂肪组织TG过度水解产生的游离脂肪酸增加、过量碳水化合物导致的肝内脂肪酸合成增加，以及从血浆中摄取的乳糜微粒和极低密度脂蛋白的贡献，当肝脏脂质储存和清除率之间出现不平衡时，会导致肝脂肪变性，进而可能发展为脂肪性肝炎、脂肪性肝硬化等严重阶段[10]。尽管已有研究表明，通过调整饮食和增加运动能够有效治疗NAFLD，但目前的治疗干预措施在实际操作中往往难以实现长期的持续效果[11]。

达格列净能够有效阻断肾脏重新吸收葡萄糖的过程，从而防止葡萄糖在体内过度累积，有助于精确调控患者的血糖水平，并促进胰岛细胞功能的改善[12]。据研究显示，SGLT2治疗，能够有效减少肝脏脂肪含量，进而改善肝功能，且肝脏脂肪含量的降低程度与体质量变化以及HOMA-IR的改善呈现出正相关关系；对于被诊断为T2DM和NAFLD/非酒精性脂肪性肝炎的患者来说，SGLT2i类药物可能是首选治疗方案[13]。研究表明，在T2DM伴随NAFLD的患者群体中，DPP-4的水平普遍升高，表明其在这些疾病的发病机理中发挥着关键作用，因此，DPP-4被视为治疗T2DM合并NAFLD的潜在靶点[14]。西格列汀作为一种DPP-4抑制剂，因其卓越的血糖调控能力和良好的安全性，被建议作为糖尿病的首选替代治疗药物，此类药物通过优化胰岛素敏感性并减轻炎症反应，展现出对心血管系统的保护作用[15]。本研究表明，采用西格列汀联合达格列净治疗的联合组，在降低血糖方面的效果较单用达格列净更为显著，与既往研究结果一致[16]。同时HOMA-IR水平均显著下降，表明胰岛素抵抗得到改善；同时，HOMA-β水平显著增加，说明胰岛β细胞功能有所恢复。并且，联合组在改善HOMA-IR和提升HOMA-β方面的表现均优于常规组，与相关报道观点一致[17]，进一步证明西格列汀联合达格列净治疗T2DM的优越性和综合效益，但是鲜见将该两个药物联合用于T2DM合并NAFLD的研究。同时，血脂异常也是NAFLD与T2DM的共同病理特征之一，本研究采用联合治疗的患者TG、TC、LDL-C水平均明显低于常规组，而HDL-C水平则显著高于常规组，表明SGLT2抑制剂和DPP-4抑制剂联合用药在调节T2DM患者的脂质代谢方面具有显著优势[18]。ALT在血液中的正常含量相对较低，当肝细胞受损，

ALT会迅速从细胞内释放到血液中，从而在短时间内引起血液中ALT水平的显著上升[19]。γ-GT主要源自肝脏，肝内或肝外胆管的阻塞会导致血液中γ-GT的浓度升高[20-21]。当肝细胞受损坏死时，原本存在于胞浆内的AST会被释放到血液中，进而引起血清中AST水平明显升高[22]。本研究治疗后两组患者的肝功能指标，包括AST、γ-GT、ALT，均展现出明显的降低趋势，表明两种治疗方案均对改善肝功能产生积极影响，且联合组优于常规组。达格列净具有抗炎、抗氧化作用，可减轻肝脏炎症反应[23]；西格列汀则通过调节GLP-1信号通路，间接改善肝脏微环境[5]。既往研究已证实SGLT2抑制剂和DPP-4抑制剂分别对NAFLD具有肝脏保护作用[24]，但二者联合治疗对NAFLD肝脏功能的影响在临床实践及机制的探讨上，尚待展开。

综上所述，西格列汀与达格列净的联合应用在治疗T2DM合并NAFLD方面展现出有效性，发挥了多重机制的协同作用，包括改善胰岛素抵抗、调节糖脂代谢以及减少肝功能损伤。在未来的研究中，需要更深入地探讨西格列汀与达格列净联合疗法的长期安全性和副作用；进一步进行NAFLD的分层分析，不仅限于观察SGLT2抑制剂和DPP-4抑制剂联合对血清肝功能指标的影响，还要探讨其对肝脏脂肪含量及纤维化的作用，以获得更确切的优化的T2DM合并NAFLD的治疗策略。

利益冲突　无

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