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Original Article

Lipid level stabilization following combination therapy with IdaGlar and Semaglutide in type 2 diabetes: a retrospective study

Fangfang Li, Junmiao Li, Jie Liu

Internal Medicine Department, Shunyi Maternal and Children's Hospital of Beijing Children's Hospital, Beijing 101300, China

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Abstract: Objective: To evaluate the clinical efficacy and lipid metabolism impact of intensified treatment with degludec-aspart dual insulin combined with semaglutide in patients with type 2 diabetes. Methods: A systematic comparison and analysis were conducted on the changes in glycolipid metabolism-related indicators (including fasting blood glucose, glycated hemoglobin, fructosamine, and 2-hour postprandial blood glucose), blood glucose fluctuation indicators (specifically including standard deviation of blood glucose, postprandial blood glucose fluctuation amplitude, and 24-hour average blood glucose), insulin function status indicators (serum insulin level, fasting C-peptide (FCP), and 2-hour postprandial C-peptide (2hCP)), insulin resistance index, visceral fat index, and lipid index (including total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) between the two groups of patients. Additionally, the adverse reactions and their incidence rates during the treatment period were statistically analyzed. Results: Before treatment, there was no significant difference in glycolipid metabolism indicators, blood glucose fluctuation, insulin function and resistance index, visceral fat index, or lipid indicators between the two groups (all $P > 0.05$). After treatment, these indicators in both groups improved compared to before treatment, and the observation group showed significantly better outcomes than the control group (all $P < 0.05$). Moreover, there was no =significant difference in the incidence of adverse reactions between groups ($P=0.576$). Conclusion: Intensified treatment with degludec-aspart dual insulin combined with semaglutide could improve blood glucose control, enhance insulin function, stabilize lipid levels, and did not increase treatment-related adverse reactions.

Keywords: Type 2 diabetes, insulin degludec-aspart, semaglutide, clinical efficacy, adverse events

Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disease in endocrine clinics and is prevalent worldwide [1, 2]. Researchers reported that China has the largest diabetic population globally, and its incidence continues to rise, making it a significant public health issue [3, 4]. Currently, the clinical management of type 2 diabetes (T2DM) follows a comprehensive strategy centered on blood glucose control. On the basis of intensive lifestyle interventions, treatment plans also cover multiple targets, including blood pressure reduction, lipid regulation, and antiplatelet therapy, aiming to comprehensively prevent cardiovascular risk and related complications, and improve patient outcome [5].

At present, diabetes glucose-lowering treatment is primarily based on supplemental exogenous insulin. Clinical studies have shown that insulin degludec/insulin aspart has dual effects on basal and prandial glycemic control. This is an important option in insulin therapy for type 2 diabetes, characterized by simplicity, efficacy, and safety, with favorable clinical outcomes [6]. However, in clinical practice, there are shortcomings such as limited flexibility and relatively complex dose adjustments. Combining it with other hypoglycemic regimens shows promise. Furthermore, studies have confirmed that com-

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bining insulin degludec/insulin aspart with semaglutide for the treatment of type 2 diabetes can achieve ideal glycemic control, but research on its effects on lipid metabolism is still limited [7, 8]. This gap in knowledge is of critical importance, given that dyslipidemia is a common comorbidity in T2DM and a major driver of cardiovascular disease - the leading cause of morbidity and mortality in this population. While glycemic control remains a primary treatment target, the holistic management of T2DM must also address lipid abnormalities to mitigate long-term cardiovascular risk. Currently, few studies have systematically investigated the lipid-modifying effects of the IDegAsp and semaglutide combination, particularly in clinical settings. Therefore, this study was designed to comprehensively evaluate the therapeutic efficacy of insulin degludec-aspart combined with semaglutide from the perspective of lipid metabolism, aiming to provide theoretical support for its use.

Patients and methods

Case selection

Data of 141 patients with type 2 diabetes treated in our hospital between January 2022 and December 2024 were retrospectively collected. According to treatment regimen, patients were divided into an observation group (insulin degludec-aspart combined with semaglutide, n=72) and a control group (semaglutide monotherapy, n=69). This study was reviewed and approved by the Ethics Committee of Shunyi Maternal and Children's Hospital of Beijing Children's Hospital (Approval No. RGSZYYLL2020013).

Inclusion criteria: (1) meeting the latest diagnostic criteria for type 2 diabetes, including persistently elevated blood glucose levels, insulin resistance, and impaired pancreatic β-cell function [9]; (2) body mass index (BMI) > 18 kg/m^2; (3) baseline C-peptide ≥ 1.0 ng/ml and fasting insulin ≥ 10 μIU/ml; (4) HbA1c level between 7% and 10%; (5) no treatment-related problems during the study period. Exclusion criteria: (1) confirmed type 1 diabetes or diabetic ketoacidosis; (2) concomitant severe cardiovascular disease; (3) significant hepatic dysfunction, defined as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels exceeding twice the upper limit of normal; (4) renal insufficiency (eGFR < 60 ml/min); (5) severe infection or ongoing anti-infective therapy; (6) pregnancy or lactation; (7) incomplete clinical data.

Treatment protocol

Both groups received routine endocrinology treatment, including diet management, exercise intervention, and regular follow-up. Dietary guidance advised patients to control the intake of food with high sugar and fat, while increase the intake of vegetables, fruits, whole grains and high protein. The exercise program required at least 150 minutes of moderate intensity aerobic activities every week, such as brisk walking, swimming or cycling. During the study, uniformly trained medical staff were responsible for the medication operation and adverse reaction records to ensure the standardization of treatment methods and the consistency of data collection.

In the control group, patients received semaglutide monotherapy (Novo Nordisk a/s, sj20210014, 1.34 mg/ml) by subcutaneous injection. The initial dose was 0.25 mg once a week, which could be gradually adjusted according to the patient's tolerance and blood glucose control.

In the observation group, patients were treated with semaglutide combined with insulin degludec-aspart injection. The drug source, administration route and dose adjustment strategy of semaglutide were exactly the same as those of the control group. Insulin degludec-aspart (Novo Nordisk a/s, j2019001, each 3 ml solution contains 300 units of insulin) was administered subcutaneously twice a day, before breakfast and dinner, with an initial total daily dose of 0.6 units/kg body weight, and subsequently adjusted according to the patient's blood glucose monitoring results. The treatment schemes of the two groups were continuously implemented for 12 weeks.

Data collection

Primary outcomes: Glucose metabolism indicators included: fasting plasma glucose (measured by fingertip or venous blood using a glucometer), glycated hemoglobin (HbA1c; determined from whole blood samples by chromatography), fructosamine (assayed enzymatically

Table 1. Comparison of baseline data between the two groups of patients

Indicator	Observation group (n=72)	Control group (n=69)	t/χ^2	P
Gender (male/female, n)	38/34	35/34	0.050	0.823
Age (years)	52.3 ± 8.7	51.6 ± 9.2	0.476	0.635
Smoking history (n, %)	25 (34.71%)	22 (31.92%)	0.132	0.716
History of hypertension (n, %)	30 (41.74%)	27 (39.11%)	0.095	0.758
BMI (kg/m^2)	24.15 ± 3.24	23.82 ± 2.93	0.587	0.558
Course of the disease (years)	5.25 ± 2.54	5.5 ± 2.8	-0.678	0.499
Genetic history (n, %)	15 (20.82%)	12 (17.42%)	0.277	0.599

from serum samples), and 2-hour postprandial blood glucose (measured by glucometer 2 hours after meal ingestion). Glycemic variability was assessed by calculating the standard deviation of multiple blood glucose measurements, postprandial glycemic excursion (difference between maximum and minimum postprandial glucose levels), and 24-hour mean glucose (obtained from the average of capillary glucose levels measured every 2 hours over a 24-hour period). Insulin resistance and adiposityindices included fasting insulin (FINS, measured by latex immunoturbidimetry), homeostasis model assessment of insulin resistance (HOMA-IR = FPG × FINS/22.5) [10]; fasting C-peptide (FCP) and 2-hour postprandial C-peptide (2hCP) measured by chemiluminescence, and visceral adiposity index assessed by body composition analyzer or abdominal CT-based fat area calculation. Lipid indices, including triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), were measured using an automated biochemical analyzer.

Secondary outcomes: To systematically evaluate treatment safety, adverse events occurring during therapy were specifically monitored and recorded in both groups. The primary adverse events of interest included three categories: (1) gastrointestinal reactions, such as nausea, vomiting, abdominal distension, or diarrhea; (2) hypoglycemic episodes, defined as abnormally low blood glucose levels potentially induced by treatment and accompanied by relevant clinical symptoms; and (3) hepatic and renal dysfunction, determined by abnormal elevations in key biochemical values, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr), or blood urea nitrogen (BUN) during the treatment period. Comparisons of the incidence of these adverse events between groups were conducted to assess differences in safety across treatment regimens.

Statistical analysis

All data were processed and analyzed using SPSS version 23.0. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation (Mean ± SD) and independent-samples t-tests were used for analysis. Categorical variables were expressed as case numbers and percentages [n (%)], and chi-square test was used for comparison. A two-tailed P value < 0.05 was considered significant.

Results

Baseline characteristics

There was no significant difference between groups in terms of age, body mass index (BMI), sex distribution, smoking history, alcohol consumption, history of hypertension, or family history of diabetes (all P > 0.05). These findings indicate that the two groups were well balanced before treatment, providing a reliable basis for subsequent evaluation of therapeutic outcomes (**Table 1**).

Comparison of hepatic and renal function, serum albumin, and total protein between groups

There was no significant difference between the two groups in liver function indices (ALT/AST), renal function indicators (Scr/BUN), serum albumin, or total protein (all P > 0.05). Preoperative imaging (color Doppler and abdominal ultrasound) revealed no pancreatic abnormalities in the diabetic patients. Additionally, post-treatment pancreatic structure remained unchanged in both groups (**Table 2**; **Figure 1**).

Table 2. Comparison of liver and kidney functions and protein levels

Indicator	Observation group (n=72)	Control group (n=69)	Statistical value	P
ALT (U/L)	24.43 ± 8.60	24.72 ± 8.70	-0.196	0.845
AST (U/L)	25.44 ± 8.12	25.35 ± 8.03	0.070	0.944
Scr (μmol/L)	79.82 ± 4.71	79.52 ± 4.51	0.368	0.714
BUN (mg/dl)	11.50 ± 2.42	11.75 ± 2.62	-0.452	0.652
TP (g/L)	73.54 ± 4.04	72.92 ± 4.43	0.808	0.421
Alb (g/L)	38.63 ± 1.93	38.84 ± 2.05	-0.580	0.563

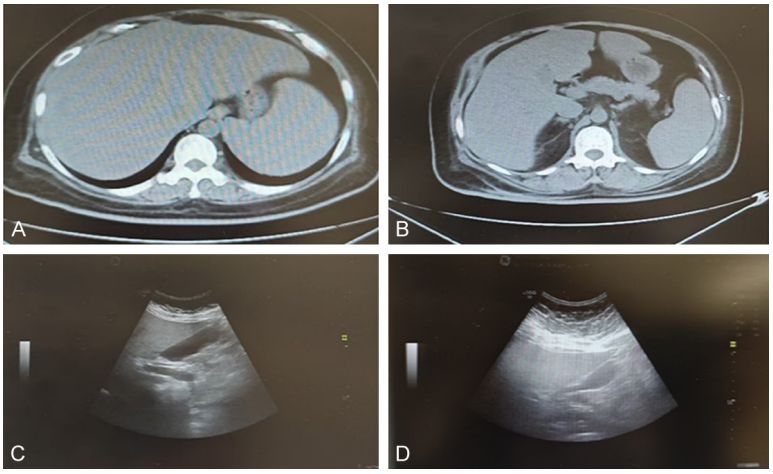

Figure 1. Representative images of pancreatic B-ultrasound and CT examinations from the two groups of patients. A, C. Before treatment; B, D. After treatment.

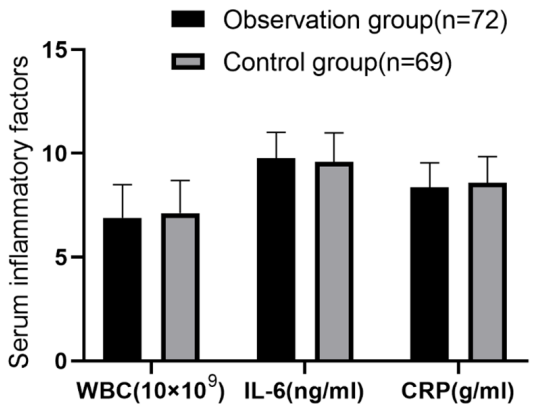

Figure 2. Comparison of preoperative blood glucose fluctuations between the two groups of patients.

Comparison of preoperative peripheral blood inflammatory markers between groups

As shown in **Figure 2**, preoperative peripheral blood inflammatory and immune-related markers were compared between the two groups. Statistical analysis showed no significant intergroup differences in baseline C-reactive protein (CRP), interleukin-6 (IL-6), or peripheral white blood cell (WBC) levels (all $P > 0.05$), indicating the groups were comparable.

Comparison of blood glucose levels between groups

After treatment, both groups showed significant reductions in fasting plasma glucose, HbA1c, fructosamine, and 2-hour postprandial glucose levels compared to their respective baseline values (all $P < 0.05$). However, no significant differences were observed between the observation group and the control group after treatment (all $P > 0.05$, **Table 3**).

Comparison of glycemic variability between groups

After treatment, both groups exhibited reductions in blood glucose standard deviation, postprandial glycemic excursion, and 24-hour mean glucose levels and the observation group showed significantly lower levels in these indices compared to the control group (all $P < 0.05$, **Figure 3**).

Comparison of pancreatic β-cell function and visceral fat index between groups

After treatment, both groups showed improvements in pancreatic β-cell function, insulin resistance, and body composition, as evidenced by reductions in fasting C-peptide (FCP), 2-hour postprandial C-peptide (2hCP), homeostasis model assessment of insulin resistance (HOMA-IR), and visceral fat index

Table 3. Comparison of blood glucose fluctuation indicators between the two groups

Indicator	Observation group (n=72)	Control group (n=69)	t	P
Fasting blood glucose (mmol/L)				
Before treatment	8.52 ± 1.41	8.49 ± 1.35	0.112	0.911
After treatment	6.88 ± 0.92*	6.91 ± 0.87*	0.178	0.859
HbA1c level (%)				
Before treatment	8.31 ± 0.79	8.28 ± 0.82	0.195	0.846
After treatment	7.02 ± 0.51*	7.05 ± 0.48*	0.326	0.745
Fructosamine (mmol/L)				
Before treatment	3.52 ± 0.39	3.54 ± 0.37	0.284	0.777
After treatment	2.78 ± 0.42*	2.75 ± 0.39*	0.392	0.696
2-hour postprandial blood glucose (mmol/L)				
Before treatment	12.22 ± 2.57	12.19 ± 2.63	0.059	0.953
After treatment	8.27 ± 1.85*	8.31 ± 1.79*	0.115	0.909

Note: Compared to before treatment, *P < 0.05.

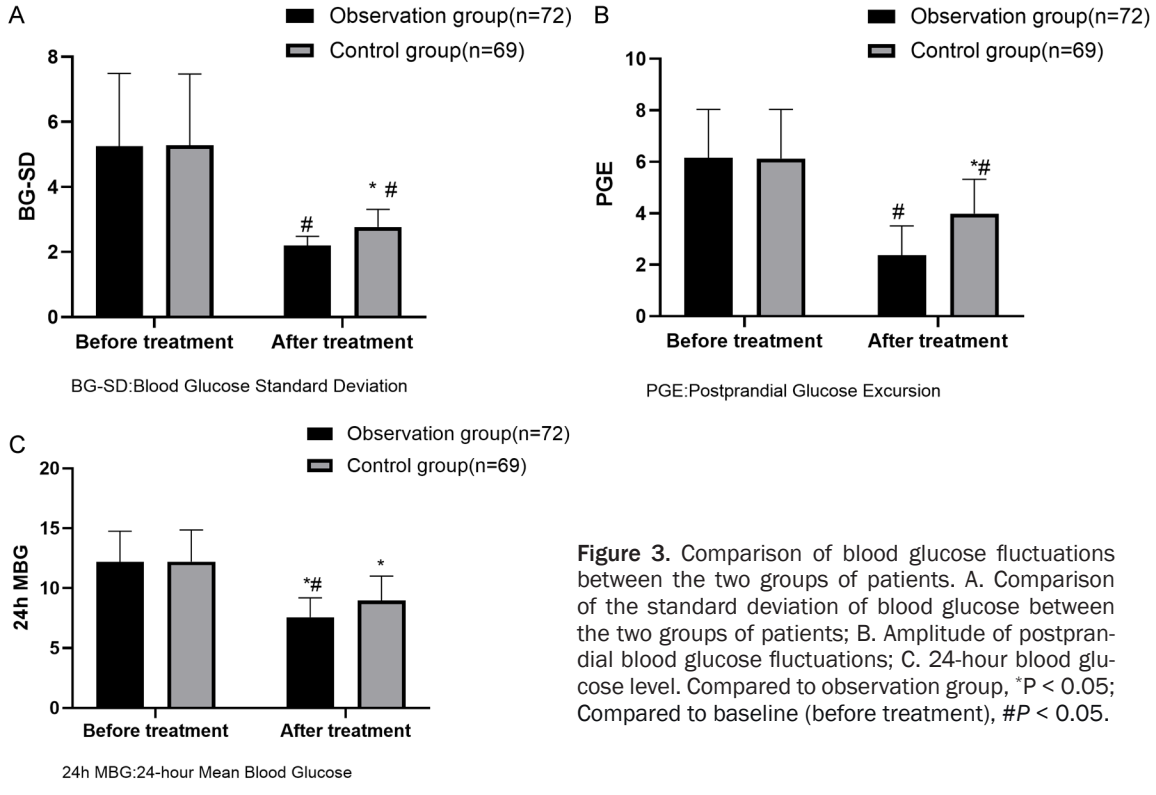

Figure 3. Comparison of blood glucose fluctuations between the two groups of patients. A. Comparison of the standard deviation of blood glucose between the two groups of patients; B. Amplitude of postprandial blood glucose fluctuations; C. 24-hour blood glucose level. Compared to observation group, *P < 0.05; Compared to baseline (before treatment), #*P* < 0.05.

compared to baseline. Further intergroup comparisons demonstrated that the observation group experienced significantly greater decreases in these indices than the control group (all P < 0.05), indicating that the combination therapy had a more pronounced effect on improving pancreatic β-cell function, reducing insulin resistance, and decreasing visceral fat (**Figure 4**).

Comparison of lipid metabolism parameters between groups

Before treatment, there were no significant differences between the two groups in lipid metabolism indices (TG, HDL-C, TC, LDL-C). After treatment, both groups showed reductions in TG, HDL-C, TC, and LDL-C compared to baseline, greater in the observation

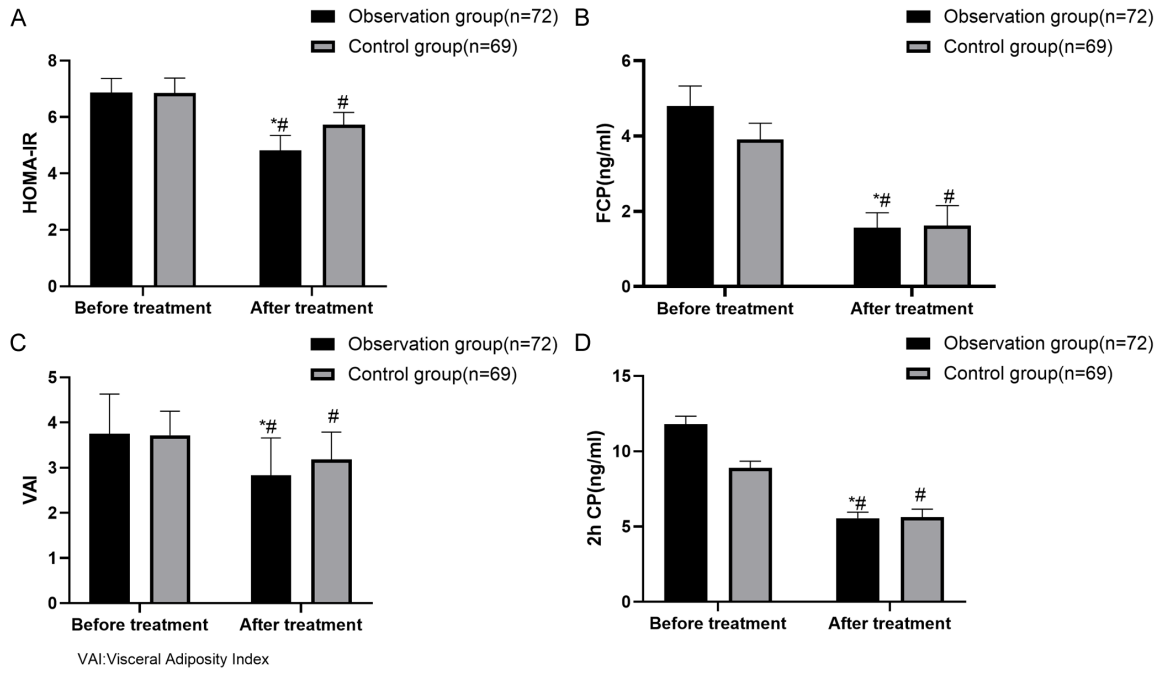

Figure 4. Comparison of pancreatic islet function before and after treatment in the two groups of patients. A. Comparison of HOMA-IR between the two groups of patients; B. Comparison of FCP between the two groups; C. Comparison of VAI between the two groups; D. Comparison of 2 h CP between the two groups. Compared to observation group, $^{*}P < 0.05$; Compared to baseline (before treatment), $\#P < 0.05$.

group than the control group (all $P < 0.05$, **Table 4**).

Comparison of adverse event incidence between groups

There was no significant difference in the overall incidence of adverse events between the two groups ($P > 0.05$, **Table 5**). These findings indicate that both treatment regimens had comparable safety profiles and tolerability.

Discussion

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder resulting from the interaction of genetic and environmental factors [11, 12]. The latest International Diabetes Federation (IDF) data show that over 500 million adults worldwide suffer from diabetes, of whom 90%-95% are type 2 diabetes [13]. The main pathogenesis of diabetes is insulin resistance and islet β cell dysfunction. In addition, obesity (especially visceral fat accumulation), sedentary lifestyle, poor dietary habits (such as high sugar and fat diet), aging, and hypertension are all important risk factors for type 2 diabetes [15, 16]. At present, the treatment of diabetes mainly relies on exogenous insulin, so how to simulate the insulin secretion mode of the normal physiologic state is an important consideration to improve treatment effect [14]. Insulin degludec-aspart is a compound preparation composed of long-acting insulin and fast acting insulin. Its role is to more accurately simulate physiologic insulin secretion, so as to achieve more stable and comprehensive blood glucose control. Semaglutide, a tyrosine kinase receptor agonist, can promote the release of insulin, and then reduce blood glucose. This drug is widely used in the treatment of type 2 diabetes, and can improve insulin sensitivity and blood glucose regulation [17, 18]. We hypothesize that using both together may provide patients with a better therapeutic outcome.

The results of this study demonstrated that patients receiving insulin degludec-aspart showed significant improvements in both glycemic control and glycemic stability compared to baseline. These findings are consistent with those reported by Heise et al., who also observed sustained glycemic stabilization with insulin degludec-aspart in a multinational trial

Table 4. Comparison of blood lipid levels before and after treatment between the two groups of patients

Indicator	Time	Observation group (n=72)	Control group (n=69)	t	P
TG (mmol/L)	Before treatment	2.84 ± 0.39	2.81 ± 0.42	0.441	0.660
	After treatment	1.42 ± 0.25*	1.80 ± 0.30*	8.135	< 0.001
TC (mmol/L)	Before treatment	5.61 ± 0.89	5.59 ± 0.94	0.130	0.897
	After treatment	3.81 ± 0.44*	4.33 ± 0.59*	6.092	< 0.001
LDL-C (mmol/L)	Before treatment	3.66 ± 0.51	3.63 ± 0.48	0.361	0.719
	After treatment	1.98 ± 0.32*	2.45 ± 0.39*	7.814	< 0.001
HDL-C (mmol/L)	Before treatment	0.97 ± 0.20	0.95 ± 0.18	0.623	0.535
	After treatment	1.34 ± 0.17*	1.16 ± 0.15*	6.873	< 0.001

Note: Compared to before treatment, *P < 0.05.

Table 5. Comparison of the incidence of adverse reactions between the two groups of patients [n (%)]

Group	Case	Gastrointestinal reaction	Hypoglycemia	Dizziness	Others	Overall incidence rate
Observation group (n=72)	72	8 (11.11)	5 (6.94)	3 (4.17)	2 (2.78)	18 (25.00)
Control group (n=69)	69	7 (10.14)	4 (5.80)	4 (5.80)	3 (4.35)	18 (26.09)
χ^2	-	0.038	0.081	0.177	0.157	0.023
P	-	0.846	0.776	0.674	-	-

[19]. The underlying mechanism can be explained as follows: insulin degludec-aspart is a combination of basal insulin degludec and rapid-acting insulin aspart, providing the dual advantages of long-acting stability and rapid postprandial glucose reduction. Insulin degludec forms soluble multihexameric depots subcutaneously, allowing slow and steady absorption, thereby maintaining a stable 24-hour basal insulin concentration, effectively controlling fasting glucose and reducing the risk of nocturnal hypoglycemia. Insulin aspart can take effect quickly, simulate physiologic insulin secretion during meals, and significantly reduce postprandial blood glucose fluctuations [20]. The two components act synergistically to more comprehensively simulate the physiologic insulin secretion mode of human body and realize the optimal management of blood glucose throughout the day. In addition, the preparation can effectively promote glucose use, inhibit hepatic glycogen output, and further improve the overall state of glucose metabolism, so as to comprehensively improve the stability and target rate of blood glucose control. This is consistent with previous research [21].

We also found that the blood glucose control level and stability of the observation group were significantly optimized compared to those of the control group after the addition of semaglutide. This aligns with the SUSTAIN clinical trial program, which consistently demonstrated a superior efficacy of semaglutide in HbA1c reduction and weight management compared to other glucose-lowering agents [22]. The underlying mechanisms are as follows: as a glucagon-like peptide-1 (GLP-1) receptor agonist, the hypoglycemic mechanism of semaglutide involves multiple pathways. First, it can stimulate insulin secretion in a glucose concentration-dependent manner and inhibit glucagon release, thereby effectively reducing postprandial and fasting blood glucose levels. Second, the drug can delay gastric emptying, reduce the absorption rate of postprandial glucose, and help stabilize blood glucose fluctuations [23]. In addition, semaglutide can also inhibit appetite, reduce food intake, and promote weight loss through central mechanisms, thereby improving insulin sensitivity. A number of clinical and basic studies have also shown that the drug may have a protective effect on pancreatic β cell function. The above multi-channel synergy not only significantly optimizes blood glucose control, but also effectively improves blood glucose stability, bringing multiple clinical benefits to patients with type 2 diabetes, corroborating previous research results [24, 25].

In addition, the results of this study showed that the blood lipid level of the observation group was significantly lower than that of the control group, and the insulin resistance and visceral fat index of the observation group were better than those of the control group, suggesting that semaglutide may improve the blood lipid level of patients to a certain extent. Similar lipid-modifying benefits of semaglutide have been reported in the STEP trials, where participants experienced notable improvements in triglyceride and LDL-C levels accompanying weight loss [26]. These are the possible mechanisms: first, the drug can promote lipolysis and inhibit hepatic lipogenesis by activating GLP-1 receptor, significantly reducing serum triglyceride (TG) and total cholesterol (TC) levels. Second, semaglutide can reduce body weight and visceral fat accumulation, improve insulin sensitivity, indirectly correct abnormal lipid metabolism, and help reduce low-density lipoprotein cholesterol (LDL-C). In addition, some studies have shown that it can also improve the level of high-density lipoprotein cholesterol (HDL-C) and further optimize the lipid profile. These effects may be related to semaglutide delaying gastric emptying, inhibiting appetite, reducing lipid absorption, and regulating related enzyme activities and gene expression, which is consistent with previous literature [27, 28].

Finally, analysis of adverse events in the two groups showed no significant differences in incidence. This safety profile agrees with the results of Aroda et al. who also found that semaglutide in combination with basal insulin did not increase the risk of severe hypoglycemia or other major adverse events [29]. This result suggested that under the intervention conditions of this study, the safety performance of the two treatment regimens was equivalent, which further supported the clinical safety of the treatment strategy [30].

However, the study still has the following limitations: First, this study was a single center, small sample exploratory study, so the sample representation was limited, which may have affected the generalizability of the results. Second, the short follow-up time failed to evaluate the medium - and long-term efficacy and safety of the combination therapy. Third, the efficacy differences in different glycated hemoglobin stratification, BMI classification, or diabetes duration subgroups were not thoroughly explored, and the precise basis for individualized treatment was lacking. Fourth, pharmacoeconomic benefits have not been systematically evaluated, and its cost-effectiveness advantage still needs further verification. Future studies with more in-depth design and larger sample are needed to verify the findings of this study.

In summary, intensified therapy with insulin degludec-aspart combined with semaglutide can improve glycemic control, enhance pancreatic β-cell function, and stabilize lipid profiles without increasing treatment-related adverse events, thereby optimizing blood glucose management and improving patients' quality of life. However, this regimen still requires further optimization and investigation to support broader clinical use.

Disclosure of conflict of interest

None.

Address correspondence to: Fangfang Li, Internal Medicine Department, Shunyi Maternal and Children's Hospital of Beijing Children's Hospital, No. 1 Shunkang Road, Shunyi District, Beijing 101300, China. Tel: +86-010-59612298; E-mail: lifangfang6677@163.com

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