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Effect of ketogenic diet plus dulaglutide on glucose and lipid metabolism in diabetes mellitus

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Abstract: Diabetes mellitus is a chronic disease with a high incidence worldwide and exclusive drug treatment has a limited effect. To investigate the effects of a ketogenic diet combined with dulaglutide on glucose and lipid metabolism in diabetic patients, a total of 104 patients with type 2 diabetes mellitus were randomly divided into a study group (dulaglutide + ketogenic diet) and a control group (dulaglutide). The results showed that, in comparison with the control group, the blood glucose and blood lipid levels in the study group were lower than those in the control group after treatment ($P<0.05$). The insulin resistance index of the study group was decreased and the insulin sensitivity index was increased ($P<0.05$). At the 6-month follow-up, the Pittsburgh Sleep Quality Index score was lower and the quality of life was better in the study group ($P<0.05$). In conclusion, thevketogenic diet combined with dulaglutide can effectively improve glucose and lipid metabolism, insulin function and quality of life in diabetes mellitus patients.

Keyword: Diabetes mellitus; Dulaglutide; Glycolipid metabolism; Ketogenic diet

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INTRODUCTION

Currently, there are about 150 million diabetes mellitus (DM) patients worldwide and the number of new cases is increasing at a rate of 12.7 million per year, with an average incidence rate up to 11.2% (Darenskaya *et al.*, 2021). After the onset of DM, patients need lifelong oral administration of hypoglycemic drugs to alleviate DM progression and prevent complications (Lovic *et al.*, 2020). However, the effect of drug therapy alone is limited and long-term use of hypoglycemic drugs may trigger insulin resistance; hence, other auxiliary means are needed to ensure the therapeutic effect on DM (Ikegami *et al.*, 2022).

Dietary control for obesity is not only an important factor leading to the onset of DM but also a significant factor inducing DM complications; therefore, strict dietary control is crucial for the prognosis of patients with DM and can serve as an important cornerstone for controlling disease progression (Chen *et al.*, 2023). Ketogenic diet (KD) is a kind of dietary pattern with high fat, moderate protein and very low carbohydrate (Norwitz *et al.*, 2020). Its core mechanism is to strictly restrict carbohydrate intake (usually <50g/ day or 5-10% of total energy), forcing the body's metabolism to switch from mainly relying on glucose to relying on ketone bodies produced by lipolysis for energy, so as to simulate metabolic changes in a starvation state (Dashti *et al.*, 2021). This metabolic switch is thought to help improve insulin sensitivity, promote fat movement and reduce body weight (Choy & Louie, 2023). Dulaglutide (DU), a novel hypoglycemic drug in clinical practice, achieves hypoglycemic effects by binding to glucagon and inhibiting its secretion; it also suppresses appetite, delays gastric emptying and helps to lose body weight, which is conducive to blood glucose control for patients (Yabe *et al.*, 2023). However, it has also been noted that DU use may cause more pronounced gastrointestinal reactions that can affect the health of the user (Maselli & Camilleri, 2021). This, in turn, negatively affects the treatment of patients with DM. Mechanistically, KD combined with DU may have good effects on the treatment of DM. The potent weight loss and insulin-sensitizing effects of KD may be synergistic or enhanced by the multiple glucose regulation and weight loss effects of DU, thereby potentially achieving better glycemic and metabolic control than treatment alone or standard therapy (Kosmalski *et al.*, 2023). Currently, studies on the treatment of KD plus DU in DM are rare and for the time being, we are unable to fully determine whether this treatment regimen has the potential to be a future treatment option for DM. In this context, the present study aimed to observe the effects of KD combined with DU on glucose and lipid metabolism in patients with DM, in order to provide a new alternative for the treatment of diabetes.

MATERIALS AND METHODS

Patient data

The sample size calculation was based on the change in the primary outcome measure HbA1c. Based on the previous literature (Gardner *et al.*, 2022), we expected the study group to have an additional 0.8% reduction in HbA1c

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compared with the control group, with a standard deviation of 1.0%. At least 49 patients were required to be enrolled in each group, as calculated with the use of software, e.g., PASS, with an alpha of 0.05 (two-sided) and a power of (1 - β) of 80%. Ultimately, 52 patients were enrolled in each group to allow for a dropout rate of approximately 5%. A total of 104 patients with DM admitted to the Affiliated Hospital of Hebei University from April 2022 to August 2023 were selected as study subjects. The patients were randomized and divided into a study group using KD plus DU treatment and a control group using KD plus conventional treatment (n = 52 in each group). Baseline data of the two groups were shown in Table 1, with no significant differences between them (P>0.05). Because baseline characteristics were balanced between the groups, between-group comparisons of post-treatment values were performed without adjustment for baseline. This study was to be conducted in strict accordance with the *Declaration of Helsinki*.

Inclusion and exclusion criteria

Inclusion criteria: According to the diagnostic guidelines of type 2 DM (Faselis *et al.*, 2020); patients with complete medical records; patients with high compliance; patients with clear cognition and the ability to communicate effectively. Exclusion criteria: patients complicated with immune diseases, malignant tumors, abnormal liver and kidney functions, abnormal gastrointestinal functions, etc.; patients with drug allergies; patients in pregnancy or lactating period; patients failing to participate in the whole study for any reason.

Methods

Both groups were given oral hypoglycemic drugs (Metformin, Sino-American Shanghai Squibb Pharmaceutical Co., Ltd., H20023370), 0.25 g/times, twice/d, for 3 months. During this period, the patients in the study group were given dietary control: A KD and a low-carbohydrate food should be dominant, with three meals a day in a regular way, referring to the ratio listed below: nutrients: Carbohydrates = 1/5; protein: Carbohydrates = 2/5; fat: Carbohydrates = 1-2/5. The fat consumed should be high-quality fat rich in ω-3 and the daily water intake should be > 2000 mL. Patients were encouraged to maintain moderate exercise for 30-60 minutes every day. To promote exercise adherence, patients were provided with an individualized exercise advice booklet, asked about exercise during weekly telephone calls or clinic visits and monitored and encouraged with an exercise diary or wearable device (e.g., a pedometer). For patients with movement difficulties, specific recommendations for exercise type and intensity adjustment were provided. Each 4-week period was considered a course of treatment and the treatment continued for a total of 6 courses.

Outcome measures

(1) Glucose and lipid metabolism: The glucose parameters of patients before and after treatment were measured, including fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG) and glycosylated hemoglobin (HbA1c), as well as the lipid parameters of triglyceride (TG), high/low-density lipoprotein cholesterol (HDL-C/LDL-C) and total cholesterol (TC). (2) Insulin levels were measured and a Homeostatic model assessment of insulin resistance/ sensitivity (HOMA-IR/HOMA-IS) was calculated. (3) Prognosis follow-up: Patients in both groups were followed up for 6 months. Each patient was followed up for 3 times by regular review, with an interval between two visits not more than 2 months. At the last follow-up, the Pittsburgh Sleep Quality Index (PSQI) (Park, 2020) and the MOS item short-form health survey (SF-36) (Abbasi-Ghahramanloo *et al.*, 2020) were investigated. The PSQI and SF-36 questionnaires were completed by patients under the supervision of a research nurse.

Statistical analysis

GraphPad 9.0 software was used for plotting and statistical analysis. Enumeration data were expressed as (%), with the chi-square test for comparison. Measurement data were expressed as ($\bar{x} \pm s$), with the independent t-test for inter-group comparison and the paired t-test for comparison before and after treatment. P<0.05 was considered statistically significant.

RESULTS

Glucose metabolism

After treatment, FPG, 2hPG and HbA1c of the study group and the control group were lower than those before treatment (P<0.05). The glucose metabolism parameters were compared between the two groups, which were lower in the study group after treatment (P<0.05) (Fig. 1).

Lipid metabolism

After treatment, TC, TG and LDL-C were reduced in both groups and were lower in the study group than in the control group (P<0.05); while HDL-C was elevated and was higher in the study group than in the control group (P<0.05) (Fig. 2).

Pancreas islet functions

After treatment, the HOMA-IS of the two groups was higher than that before treatment, and the HOMA-IS of the study group was higher than that of the control group (P<0.05). HOMA-IR decreased after treatment in both groups and was lower in the study group than in the control group (P<0.05) (Fig. 3).

Prognosis

All the study subjects were successfully followed up. In the study group, the score of the PSQI was (4.54±1.43), lower than that in the control group (P<0.05), while the scores of bodily function, mental function, social function and material life were higher than those in the control group (P<0.05) (Fig. 4).

Table 1: Clinical data of the two groups

Groups	n	Age	Male/female	Duration of disease (years)	Combined hypertension/no combined hypertension
Control group	52	47.56±6.12	34 (65.38%)/18 (34.62%)	4.77±1.38	22 (42.31)/30 (57.69%)
Study group	52	48.25±6.18	35 (67.31%)/17 (32.69%)	4.87±1.24	26 (50.00%)/26 (50.00%)
χ^2/t		0.574	0.043	0.374	0.619
P		0.567	0.836	0.709	0.431

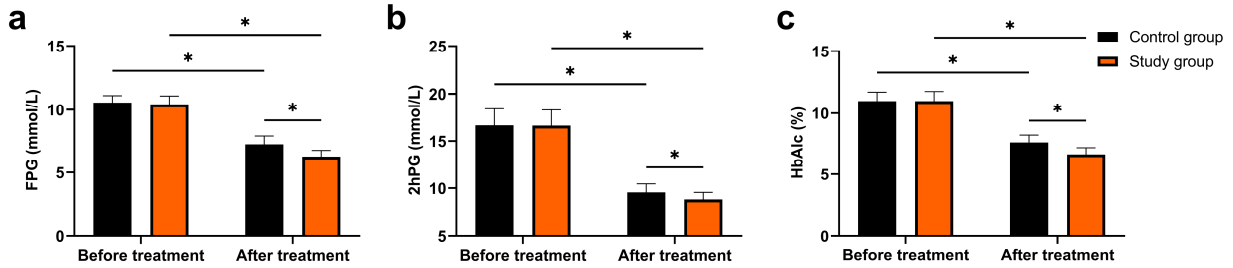

Fig. 1: Comparison of a) FPG, b) 2hPG, and c) HbA1c. * indicates P<0.05. Fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPG) and glycosylated hemoglobin (HbA1c).

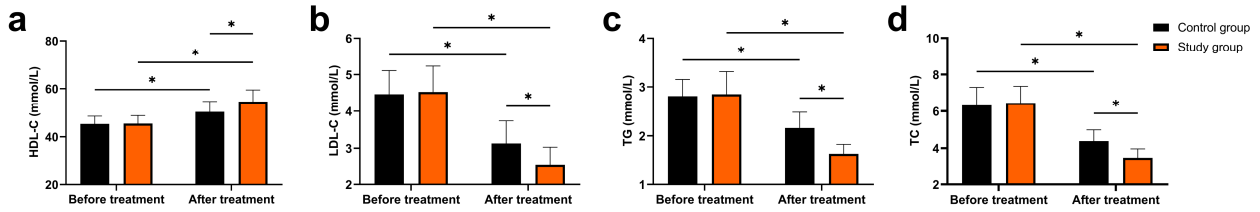

Fig. 2: Comparison of a) HDL-C, b) LDL-C, c) TG, and d) TG. * Indicates P<0.05. High/low-density lipoprotein cholesterol (HDL-C/LDL-C), triglyceride (TG) and total cholesterol (TC).

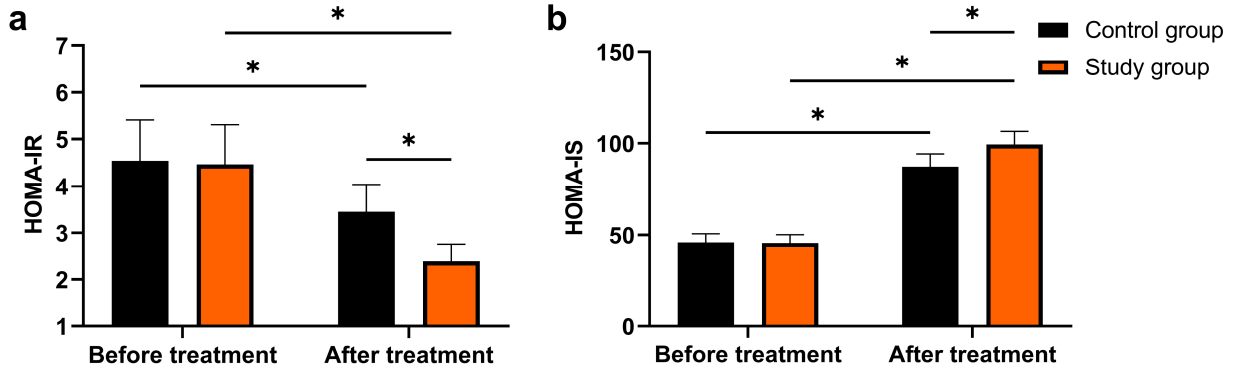

Fig. 3: Comparison of a) HOMA-IR and b) HOMA-IS. * indicates P<0.05. Homeostatic model assessment of insulin resistance/sensitivity (HOMA-IR/HOMA-IS).

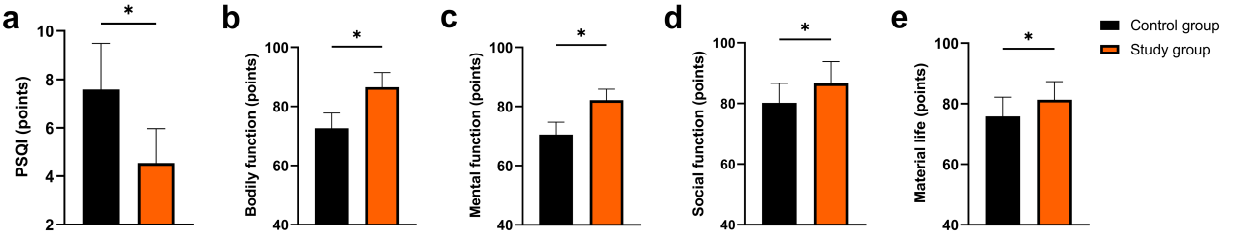

Fig. 4: Comparison of a) PSQI, b) bodily function score, c) mental function score, d) social function score and e) material life score. * Indicates P<0.05. pittsburg sleep quality index (PSQI).

DISCUSSION

Once DM occurs, it requires lifelong conservative treatment and has a significant negative impact on the patient's daily life (Fralick *et al.*, 2022). Improving the glucose metabolism in DM more effectively is a hot topic and challenge in clinical research. In this study, we analyzed the effect of the KD plus DU on DM, which is of great significance for future clinical treatment of DM.

First, we found that the KD plus DU is more effective in improving the glucose and lipid metabolism in patients with DM (Fig. 1 and Fig. 2). Dietary intervention is the simplest and most economical way to prevent the progression of DM. Previous studies have confirmed that a KD puts the body into a state of hunger, resulting in starvation ketosis, which replaces the traditional glucose-based energy supply mode with a ketone-based one; this mode promotes fat breakdown, converts insoluble triglycerides into soluble ketones and eventually eliminates them through urine, which reduces glucose and aids in weight loss; however, KDs may produce side effects such as pollakiuria, constipation, electrolyte disturbance, dizziness, fatigue, headache and diarrhea of typically mild degree, without affecting treatment (Yang *et al.*, 2023). Therefore, the addition of the dietary regimen to the conventional treatment of DM generally achieves better glucose control (Glenn *et al.*, 2023). DU, as a GLP-1 receptor agonist, when used in conjunction with the KD, not only enhances the effectiveness of diet control but also avoids the risk of lactic acidosis caused by various hypoglycemic drugs.

The study by Nauck *et al*., the amino acid sequence of DU has 90% similarity to endogenous sequences in the human body, enabling it to effectively activate GLP-1 receptors, restore pancreatic β-cell function, increase insulin release and prevent glucagon secretion and hepatic glucose output (Nauck *et al.*, 2021). These effects may contribute to better control of glucose metabolism in DM patients undergoing KD. DU can also inhibit central appetite, helping reduce food intake and delaying gastric emptying, thereby promoting weight loss (Shand *et al.*, 2023). These helpings are also more favorable for patients to follow KD therapy. Hence, DU combined with dietary control not only promotes fat metabolism, accelerates fat loss and reduces weight, but also enhances insulin sensitivity, reduces insulin resistance and lowers insulin levels. This is the reason why the HOMA-IR was lower but the HOMA-IS was higher in the study group (Fig. 3). Similarly, Zhang indicated that DU could improve insulin function in patients with polycystic ovary syndrome (Zhang *et al.*, 2023), further supporting our viewpoint.

Finally, we found that both sleep quality and quality of life improved significantly in the study group compared with the control group (Fig. 4). It has been reported that DU itself may affect patients' feelings by regulating gastrointestinal function and providing energy substrates (Attia *et al.*, 2024) and KD is likely to play an important synergistic or independent role. The following mechanisms may explain the contribution of KD: (1) More stable blood glucose levels help maintain normal circadian rhythm and neurotransmitter balance, which may improve sleep quality and continuity and reduce night awareness (Perlman *et al.*, 2024). (2) KD combined with DU resulted in significant weight loss. Weight loss, particularly visceral fat, directly improved physical function (e.g., increased activity tolerance and reduced joint burden), which coincided with improved SF-36 physical function scores. (3) Obesity and T2DM are often accompanied by chronic low-grade inflammation. KD has been shown to reduce inflammatory markers (El Karkafi *et al.*, 2023). Reductions in inflammatory status were associated with improvements in fatigue, pain and overall well-being, which may improve QOL scores. Long-term compliance of KD is a major challenge due to its strict restrictive nature. Decreased adherence may lead to attenuated or even rebound effects. Future studies with longer follow-up and more objective methods are needed to assess KD adherence and its long-term relationship with sleep /QOL. This study has several limitations. Firstly, the sample size was relatively small and recruited from a single center, which may limit the generalizability of the findings. Secondly, the open-label design (lack of blinding) could introduce potential bias, although randomization was employed. Thirdly, adherence to the ketogenic diet and exercise regimen was encouraged but not strictly monitored or measured using objective tools (e.g., food diaries, urine ketone testing, activity trackers). Fourthly, the relatively short duration of active treatment (3 months) and follow-up (6 months) may be insufficient to evaluate the long-term efficacy, safety and sustainability of the ketogenic diet plus DU regimen.

In the follow-up study, we need to carry out more in-depth and comprehensive research and analysis according to the above limitations as soon as possible. Finally, the improvement in quality of life is the result of multiple factors. In addition to KD and DU, the daily exercise encouraged in the study may also have a positive effect on sleep and QOL. Future studies should assess and report these confounders more fully.

CONCLUSION

In conclusion, KD combined with DU may have advantages in improving short-term glycemic control, lipids, insulin sensitivity and quality of life in patients with DM over a 3-month treatment period. However, these results are limited by study duration, sample size, single-center design and lack of rigorous adherence monitoring. Larger, longer, multicenter trials are needed to confirm the sustainability, long-term safety, efficacy and effect on complications of this combination therapy before definitive clinical recommendations can be made.

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Not applicable.

Authors' contributions
Yujie Gu and Minxiang Wei designed the study. Rui Gao and Lu Yan wrote the manuscript, Xuerun Du and Shuqing collected and analyzed the data. Lei Xue and Tingting Li revised the manuscript. Rui Gao and Lu Yan made equal contributions to this work as first co-authors, Yujie Gu and Minxiang Wei as co-corresponding authors. All authors read and approved the final submitted manuscript.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval
The study was approved from the Affiliated Hospital of Hebei University, Ethics Committee (HDFY-LL-2022-201).

Conflict of interest
Authors have no conflict of interest to declare.

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