


# Comparison of Effects of Glucagon-Like Peptide-1 Receptor Agonists Compared to Long-Acting Insulin, Added to Oral Anti-Diabetic Agents on Self-Management Behaviors, Anxiety, and Sleep Quality in Patients with Type 2 Diabetes

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**Aim:** This study aimed to investigate the impact of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on individuals with type 2 diabetes (T2DM) by comparing self-management behaviors, anxiety, and sleep quality in T2DM patients.

**Methods:** This is a single-center prospective study. During the patients' hospitalization, we collected their clinical data, and three months after discharge, we conducted follow-up by phone to record weight changes, blood glucose levels, self-management behaviors, anxiety levels, and sleep quality.

**Results:** A total of 271 patients were included in this study. Among them, 177 (65.31%) were classified into the oral drug combined with long-acting insulin group, and 94 (34.69%) were classified into the oral drug combined with GLP-1RAs group. No statistically significant differences were found between the two groups in age, duration of diabetes, comorbidities, complications, or types of oral medications ( $P > 0.05$ ). However, significant differences were observed between the groups in postprandial blood glucose, glycated hemoglobin, dietary control, medication adherence, actual anxiety, and sleep time ( $P < 0.05$ ). Notably, the oral medication combined with GLP-1RAs group demonstrated improved dietary control, medication adherence, anxiety and actual sleep time compared to the oral medication combined with long-acting insulin group.

**Conclusion:** In this 3-month study, there were statistically significant differences in HbA1c, post-prandial glucose, weight, for self-management behaviors, for dietary control, medication adherence, anxiety, and actual sleep time in T2DM patients. The findings suggest that GLP-1 RA may contribute to the improvement of dietary behaviors, medication adherence, anxiety, and sleep quality in addition to weight and glycemic control in T2DM patients.

**Keywords:** glucagon-like peptide-1 receptor agonist, T2DM, anxiety, sleep, self-management behavior

## Introduction

Diabetes mellitus (DM) manifests as persistent high blood sugar levels due to various causes.<sup>1</sup> In 2021, the global diabetic population numbered approximately 537 million, and the International Diabetes Federation (IDF) anticipates a surge to 783 million by 2045.<sup>2</sup> Presently, the primary clinical interventions for DM involve oral hypoglycemic agents and insulin. Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) stand out as a potent hypoglycemic agent endorsed by both the American Diabetes Association and the Chinese Medical Association Diabetes Section.<sup>3,4</sup> In recent years, GLP-1RAs

have gained more attention for their cardiovascular and renal benefits in patients with type 2 diabetes (T2DM). GLP-1RAs contribute to reduced food intake, body weight, and blood glucose levels. Current research primarily focuses on the effects of GLP-1RAs on clinical parameters such as blood glucose, blood lipids, and body weight in T2DM patients. A study that divided 180 patients with T2DM into a GLP-1RAs combined with insulin group and an insulin-only group found that the GLP-1RA combined with insulin group showed significant improvements in body weight, BMI, waist circumference, blood pressure, blood glucose, and insulin resistance.<sup>5</sup> Another meta-analysis also showed that GLP-1 receptor agonists significantly improved blood glucose control, weight management, and lipid profiles in patients with T2DM.<sup>6</sup>

Self-management behavior in diabetes patients is a core aspect of their health behavior, encompassing diet, exercise, blood glucose monitoring, foot care, and medication management. Previous studies have indicated that self-management behaviors can effectively improve blood glucose control and slow the progression or development of complications.<sup>7</sup> Diabetes is associated with complex relationships with sleep disorders and anxiety. Several meta-analyses have found that anxiety is common among diabetes patients, and the risk of anxiety disorders is increased by 41%.<sup>8</sup> Therefore, it is recommended to screen for anxiety during the initial diagnosis and follow-up of diabetes patients. Additionally, sleep problems, including poor sleep habits and sleep disorders, are prevalent among adults with T2DM.<sup>9</sup>

However, there is currently a lack of research on the self-management behavior, anxiety and sleep quality of diabetes patients treated with GLP-1RAs. Understanding the effects of antidiabetic medications on patients' self-management behaviors, anxiety, and sleep quality may help with the development of future interventions to improve treatment outcomes. This study aims to investigate whether GLP-1RAs were linked to self-management behaviors, anxiety, and sleep quality in Chinese diabetes patients.

## Materials and Methods

### Participants

A telephone follow-up was conducted for 1620 diabetic patients discharged between January and December 2022, three months post-hospital discharge. Inclusion criteria comprised: (1) age  $\geq 18$  years; (2) type 2 diabetes diagnosis based on the World Health Organization criteria (1999);<sup>10</sup> (3) use of at least one oral hypoglycemic agent, including  $\alpha$ -glucosidase inhibitors, metformin, sulfonylurea prokinetic agents, dipeptidyl peptidase-4 inhibitors, rosiglitazone, pioglitazones, and sodium-glucose co-transporter protein 2 inhibitors; (4) combined administration of either long-acting insulin or GLP-1RA (daily formulation or weekly formulation); (5) patients or immediate family members answering the phone and willing to participate in the follow-up survey. Exclusion criteria included: (1) gestational diabetes mellitus or other diabetes mellitus types; (2) other types of antidiabetic drug regimens; (3) inability to be reached by telephone after three attempts; (4) premature call disconnection; and (5) incomplete or missing data.

Ultimately, a total of 271 T2DM patients with long-acting insulin or GLP-1RA were followed up three months after their initial hospitalization.

This research has been approved by the Ethics Committee of Tongji Hospital (March 2020, approval number: TJ-IRB20200315) and fully complies with the ethical standards outlined in the Declaration of Helsinki. Informed consent and assent were obtained from all participants.

## Data Collection Instruments and Measurements

### Methods of Follow-Up

The follow-up content was pre-designed through a review of the literature and group discussions. A follow-up form was created, and a schedule for the follow-up staff was established. Follow-up was conducted three months post-discharge via telephone. With trained staff asking questions based on the follow-up form's content. A designated quality inspector was assigned on each follow-up day to review the collected data, ensuring the completeness and accuracy, with no omissions or errors.

### Observation Indicators

(1) General Observation Indicators: This category encompasses gender, age, weight, height, education level, number of comorbid underlying diseases, and diabetes medication. (2) Clinical Indicators: This includes weight change (calculated as weight at 3 months after discharge minus weight at discharge), mean fasting blood glucose, mean postprandial 2h blood

glucose, Hemoglobin A1c (HbA1c), and the number of hypoglycemia occurrences within 3 months of discharge. (3) Self-Management Behaviors: The Diabetes Self-Management Behavior Scale 6 (Summary of Diabetes Self-Care Activities-6, SDSCA-6)<sup>11</sup> was employed. It comprises six entries in five dimensions, assessing specific behaviors over the past 7 days, including dietary control, physical exercise, blood glucose monitoring, foot care, and the use of diabetes medication. Each day corresponds to 0–7 points, with a higher score indicating enhanced self-management ability. (4) Sleep Quality: The Pittsburgh Sleep Quality Index (PSQI) gauged patients' sleep quality using 3 entries for subjective sleep quality, sleep onset time, and sleep duration.<sup>12</sup> Subjective sleep quality was assessed using descriptors such as “very good, better, worse, very bad”. (5) Anxiety: The anxiety level was assessed through the Self-Rating Anxiety Scale (SAS),<sup>13</sup> which has a standard total score ranging from 0 to 100 points. A higher score indicates a more pronounced level of anxiety.

Data of demographic and clinical biochemical and diabetes-related information were obtained from Tongji Hospital's hospitalization and outpatient medical record system.

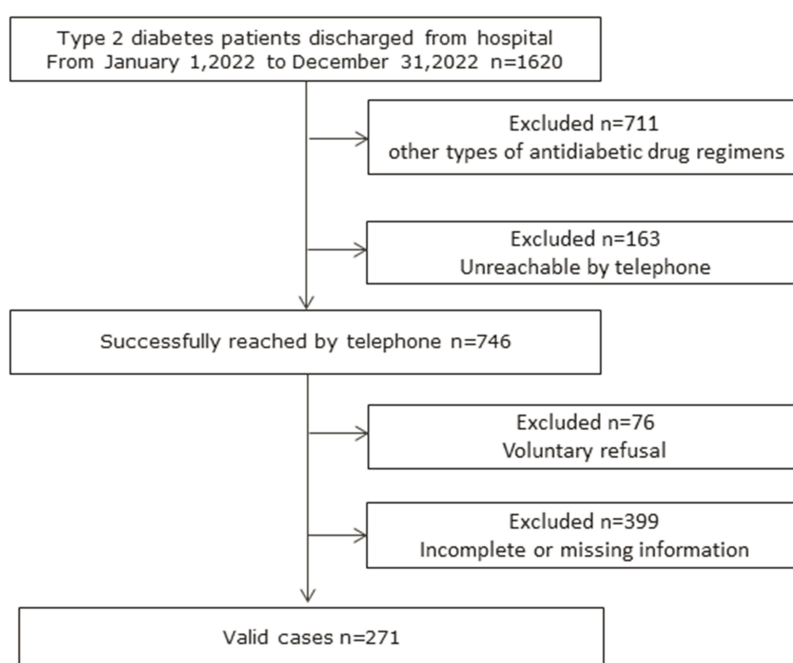
## Statistical Analysis

Data analysis was performed using SPSS 22.0 software. For measurement data, a normality test was conducted. Normally distributed data were presented as mean  $\pm$  standard deviation ( $X \pm s$ ), while non-normally distributed data were expressed as median (25th percentile, 75th percentile) [(M (P25, P75))]. Between-group comparisons employed either a two independent samples *t*-test or Mann–Whitney *U*-test for non-parametric analysis. Count data were presented as frequency or percentage, with group comparisons executed through the  $\chi$  test. A significance level of  $P < 0.05$  was considered statistically significant. Categorical data comparisons utilized the  $\chi^2$  test, with the Fisher's exact probability method applied when necessary. A significance level of  $P < 0.05$  was considered statistically significant.

## Results

### General Information of the Two Groups of Patients

The flow chart of our study is shown in Figure 1. Among the 1620 discharged patients diagnosed with T2DM, 1349 patients were excluded according to the exclusion criteria and 271 patients were enrolled in this study. The included participants were categorized into two groups based on their antidiabetic drug regimen: long-acting insulin group, and GLP-1RA group. The “long-acting insulin group” consisted of 177 patients receiving oral medication + long-acting



**Figure 1** Patient Screening Flowchart.

**Table 1** Demographic and Clinical Characteristics of the Long-Acting Insulin and GLP-1 RA Groups

Characteristics	Long-Acting Insulin Group (n=177)	GLP-1RA Group (n=94)	Statistic	P value
Gender (cases)			$\chi^2 = 0.578$	0.447
Male	115	64		
Female	62	30		
Age ( $\bar{X} \pm s$ , years)	48.51 $\pm$ 12.50	45.52 $\pm$ 12.78	$t = 1.845$	0.067
Marital status				0.108 <sup>a</sup>
Married	168	90		
Unmarried	6	4		
Divorcee	1	0		
Widowed	2	0		
Disease duration [(M (P <sub>25</sub> , P <sub>75</sub> ), years]	3.00(1.00,5.00)	1.00(0.20,9.00)	$U = -1.808$	0.071
Number of comorbidities [(M (P <sub>25</sub> , P <sub>75</sub> ), species]	2.00(1.00,3.00)	1.00(0.00,3.00)	$U = -0.761$	0.447
Number of complications [(M (P <sub>25</sub> , P <sub>75</sub> ), species]	1.00(1.00,2.00)	1.00(1.00,2.00)	$U = -1.110$	0.267
Type of oral medication [(M (P <sub>25</sub> , P <sub>75</sub> ), class]	1.00(1.00,2.00)	2.00(1.00,2.00)	$U = -0.010$	0.992
Smoking (cases)				
Yes	41	26	$\chi^2 = 0.667$	0.414
No	136	68		

Notes: Data were means  $\pm$  SEM or median (25th percentile, 75th percentile) [(M (P<sub>25</sub>, P<sub>75</sub>)] or n. <sup>a</sup>using Fisher's exact probability methodology.

insulin, with 115 males and 62 females, averaging 48.51 $\pm$ 12.50 years. The “GLP-1RA group” included 94 patients receiving oral medication + GLP-1RA, with 64 males and 30 females, averaging 45.52 $\pm$ 12.78 years. No significant differences were observed between the two groups in terms of gender, age, marital status, disease duration, number of comorbidities, number of complications, type of oral medication, or smoking (all  $p > 0.05$ ) (Table 1).

## Comparison of Clinical Indicators of Patients in Two Groups at 3 Months of Discharge From the Hospital

Statistical analysis revealed significant differences between the long-acting insulin group [0.00 (−1.65, 0.00)] and the GLP-1RA group [−1.90 (−5.00, 0.00)] in terms of weight changes ( $P < 0.001$ ). The GLP-1RA group [8.65 (7.10, 10.00)] exhibited significantly lower postprandial glucose levels compared to the long-acting insulin group [9.70 (8.00, 11.00)] ( $P < 0.001$ ). Additionally, the HbA1C in the GLP-1RA group [11.06 (9.80, 11.75)] was lower than that in the long-acting insulin group [11.44 (10.43, 12.95)] ( $P < 0.05$ ). Conversely, no statistically significant differences were observed in fasting blood glucose and the number of hypoglycemia occurrences between the two groups (all  $P > 0.05$ ) (Table 2).

**Table 2** Comparison of Clinical Indicators of the Long-Acting Insulin and GLP-1 RA Groups at 3 Months Post-Discharge

Characteristics	Long-Acting Insulin Group (n=177)	GLP-1RA Group (n=94)	Statistic	P value
Change in weight [(M (P <sub>25</sub> , P <sub>75</sub> ), kg]	0.00 (−1.65,0.00)	−1.90 (−5.00,0.00)	$U = -4.239$	<0.001
Fasting blood glucose [(M (P <sub>25</sub> , P <sub>75</sub> ), mmol/L]	6.00(5.60,6.00)	6.00(5.50,7.00)	$U = -0.490$	0.624
Postprandial blood glucose [(M (P <sub>25</sub> , P <sub>75</sub> ), mmol/L]	9.70(8.00,11.00)	8.65(7.10,10.00)	$U = -3.771$	<0.001
HbA1C [(M (P <sub>25</sub> , P <sub>75</sub> ), %]	11.44 (10.43,12.95)	11.06 (9.80,11.75)	$U = -2.878$	0.004
Number of hypoglycemic episodes [(M (P <sub>25</sub> , P <sub>75</sub> ), episodes]	0.00(0.00,0.00)	0.00(0.00,0.00)	$U = -1.343$	0.179

Notes: Data were median (25th percentile, 75th percentile) [(M (P<sub>25</sub>, P<sub>75</sub>)].

## Comparison of Patients' Self-Management Ability at 3 months After Discharge Between the Two Groups

Patients in the GLP-1RA group exhibited superior dietary and medication management behaviors compared to those in the long-acting insulin group ( $P < 0.05$ ). However, no statistically significant differences were observed in the total scores of exercises, glucose monitoring, foot care, or overall self-management skills between the two groups ( $P > 0.05$ ) (Table 3).

## Comparison of Anxiety and Sleep Quality Between the Two Groups of Patients

Statistical analysis revealed a significant difference in anxiety scores between patients in the GLP-1RA group and the long-acting insulin group ( $P < 0.001$ ). Furthermore, actual sleep time in the GLP-1RA group was longer than that in the long-acting insulin group ( $P < 0.05$ ). However, the differences in the time taken to fall asleep and sleep ratings were not statistically significant between the two groups (Table 4).

## Discussion

### GLP-1RA Facilitates Weight Control and Lowers Patients' Blood Glucose Levels

GLP-1RA has been demonstrated to enhance postprandial insulin secretion, diminish glucagon production, prolong gastric emptying, induce satiety, and reduce food intake, consequently lowering postprandial blood glucose.<sup>14</sup> The statistically significant difference in postprandial blood glucose between the GLP-1RA and insulin groups aligns with the expected outcomes based on the mechanism of action of GLP-1RA. The HbA1c in the GLP-1RA group was notably lower than that in the insulin group ( $P < 0.05$ ), indicating superior glycemic control in the GLP-1RA group. Given the real-world nature of this study on diabetic patients using GLP-1 medication, missing values for glycated hemoglobin were excluded. Although glycated hemoglobin is the gold standard for reflecting long-term glycemic control, future studies should strive to increase the frequency of glycated hemoglobin detection for a more objective assessment of glycemic control. The statistically significant difference in weight change between the GLP-1RA and long-acting insulin groups ( $P < 0.001$ ) is in line with findings from a large double-blind study.<sup>15</sup> In that study, adults with a BMI  $>30\text{kg}/\text{m}^2$

**Table 3** Comparison of Patients' Self-Management Ability at 3 Months Post-Discharge Between the Long-Acting Insulin and GLP-1 RA Groups

Characteristics	Long-Acting Insulin Group (n=177)	GLP-1RA Group (n=94)	Statistic	P value
Dietary control [(M (P <sub>25</sub> , P <sub>75</sub> ), points]	7.00(5.00,7.00)	7.00(7.00,7.00)	$U=-2.957$	0.003
Sports and exercise [(M (P <sub>25</sub> , P <sub>75</sub> ), points]	7.00(5.00,7.00)	7.00(7.00,7.00)	$U=-0.417$	0.677
Glucose monitoring [(M (P <sub>25</sub> , P <sub>75</sub> ), points]	2.00 (1.75,4.00)	2.00 (1.75,4.25)	$U=-0.908$	0.364
Foot care [(M (P <sub>25</sub> , P <sub>75</sub> ), points]	0.00(0.00,7.00)	3.00(0.00,7.00)	$U=-0.943$	0.346
Medication [(M (P <sub>25</sub> , P <sub>75</sub> ), points]	7.00(7.00,7.00)	7.00(7.00,7.00)	$U=-2.430$	0.015
Total [(M (P <sub>25</sub> , P <sub>75</sub> ), points]	25.25(20.75,29.63)	26.00(22.50,30.00)	$U=-1.869$	0.062

Notes: Data were median ((25th percentile, 75th percentile)) [(M (P<sub>25</sub>, P<sub>75</sub>)] or n.

**Table 4** Comparison of Anxiety and Sleep at 3 Months Post-Discharge Between the Long-Acting Insulin and GLP-1 RA Groups

Characteristics	Long-Acting Insulin Group (n=177)	GLP-1RA Group (n=94)	Statistic	P value
Anxiety [(M (P <sub>25</sub> , P <sub>75</sub> ), min]	37.50(31.25,37.50)	35.00(23.75,37.50)	$U=-3.660$	$<0.001$
Time taken to fall asleep [(M (P <sub>25</sub> , P <sub>75</sub> ), min]	30.00(20.00,30.00)	30.00(30.00,30.00)	$U=-0.015$	0.988
Actual sleep time [(M (P <sub>25</sub> , P <sub>75</sub> ), h]	7.00(6.00,7.00)	7.00(7.00,8.00)	$U=-2.625$	0.008
Sleep evaluation			$U=-2.895$	0.411 <sup>a</sup>
Excellent	29	15		
Relatively good	125	70		
Mediocre	19	8		
Poorly	4	1		

Notes: Data were median ((25th percentile, 75th percentile)) [(M (P<sub>25</sub>, P<sub>75</sub>)] or n. <sup>a</sup>using Fisher's exact probability methodology.

who did not have diabetes were randomized into a simethicone group and a placebo group. The mean weight change at the end of the intervention was  $-14.9\%$  in the simethicone group and  $-2.4\%$  in the placebo group, indicating a substantial and statistically significant difference. While this current study primarily utilized once-daily liraglutide and once-weekly dulaglutide, a weekly preparation of semaglutide was used in the referenced study. However, both are GLP-1RA preparations. According to the Chinese Guidelines for the Prevention and Control of Type 2 Diabetes Mellitus (2020 Edition),<sup>16</sup> GLP-1RA is an effective weight-lowering drug that can lower blood glucose levels and reduce the incidence of hypoglycemia. The difference in the number of hypoglycemia occurrences between the two groups in this study was not statistically significant, potentially due to challenges in timely hypoglycemia detection. The study involved home-bound patients, limiting the frequency of blood glucose measurements. Additionally, patients may not have recognized mild hypoglycemic symptoms, such as excessive sweating, weakness, and hunger, and may have alleviated these symptoms by eating. This limitation could introduce bias in the hypoglycemia information collected during follow-up.

## GLP-1RA Helps Improve Patients' Food Addiction Disorder and Develop Good Self-Management Behaviors

Patients in the GLP-1RA group demonstrated significantly better self-management behaviors in dietary practices and medication adherence compared to those in the long-acting insulin group ( $P < 0.05$ ). An animal study found that GLP-1RA improved food addiction by activating GLP-1 and modulating communication between neurons involved in rewarding behaviors.<sup>17</sup> This resulted in reduced food consumption and diminished desire for high-fat foods. Food addiction involves challenges in rational food control, including issues related to tolerance, cravings, withdrawal, and uncontrollable consumption times and amounts.<sup>18</sup> Eating behaviors, such as moderate consumption and reduced intake of high-fat or high-sugar foods, were notably better in the GLP-1RA group compared to the insulin group. This improvement may be attributed to the reduction in gastric emptying, appetite suppression, and the amelioration of food addiction disorder by GLP-1RA. Shoemaker et al<sup>19</sup> evaluated once-weekly injections of GLP-1RA in obese patients, revealing that patients in the GLP-1RA group had lower total intake, protein, and fat intake compared to the placebo group ( $P < 0.05$ ). There was no statistically significant difference in carbohydrate intake between the two groups ( $P > 0.05$ ). This suggests that GLP-1RA aids patients in managing the type and amount of food intake, aligning with the findings of this study. Medication adherence among patients in the GLP-1RA group was significantly higher than that in the insulin group. This disparity could be linked to adverse reactions such as hypoglycemia and weight gain associated with insulin injections. Grant et al<sup>20</sup> assessed treatment satisfaction using the Satisfaction with Diabetes Treatment Questionnaire, encompassing dimensions such as satisfaction with the current treatment, convenience, flexibility, knowledge of diabetes, willingness to recommend the current treatment regimen, and intention to continue the current treatment regimen. Results showed that patients in the exenatide group had higher treatment satisfaction than those in the insulin group ( $P < 0.05$ ). There was no statistically significant difference between the GLP-1RA and insulin groups in terms of exercise. Shoemaker's study also reported no significant difference in the daily time spent on light, medium, or heavy activity between the GLP-1RA group and the placebo group.<sup>19</sup> This indicates that GLP-1RA does not affect patients' physical exercise, consistent with the current study. Furthermore, there was no statistically significant difference between the two groups in terms of blood glucose monitoring, the number of days of foot care, and smoking. This lack of difference may be attributed to the habits of diabetic patients, who may not alter their habits in terms of blood glucose monitoring, foot care, or smoking due to GLP-1RA injections.

## GLP-1RA Effectively Improves the Sleep and Anxiety Status of Diabetic Patients and Enhances the Quality of Life

The actual sleep time of patients in the GLP-1RA group was longer than that of the long-acting insulin group. However, there was no statistically significant difference between the two groups in terms of time to sleep and subjective evaluation of sleep. This observation may be associated with the reduced hunger/appetite or weight loss caused by GLP-1RA.<sup>21,22</sup> You Jiaxin et al conducted a meta-analysis based on 13 randomized controlled studies to explore the effects of GLP-1RA on sleep in patients with T2DM and obstructive sleep apnea hypopnea syndrome.<sup>23</sup> The results indicated that patients in

the GLP-1RA group had a lower sleep apnea index, higher nocturnal sleep oxygen saturation levels at the lowest point of oxygen saturation, and fewer nocturnal awakenings, leading to an overall improvement in sleep quality. The anxiety level of patients in the GLP-1RA group was significantly lower than that of the long-acting insulin group and long-term diabetes mellitus patients. GLP-1RA exhibited an anxiety-reducing effect, possibly through a direct impact of the drug or an indirect positive effect resulting from the effective glycemic control achieved by GLP-1RA. The reasons for the reduction in anxiety have not been extensively studied. Grant et al investigated the effects of GLP-1RA on the psychology and quality of life of patients, finding a significant improvement in patients' anxiety status, aligning with the outcomes of the present study.<sup>20</sup> Anxiety and depression states, as well as binge eating, interact with each other.<sup>24</sup> GLP-1RA demonstrated the ability to enhance patients' dietary management behaviors and reduce anxiety states. Healthy eating behaviors and a positive psychological state can mutually reinforce each other, generating positive effects that contribute to an improved quality of life. Additionally, some studies have reported a positive correlation between sleep quality and anxiety-depression scores in remote workers.<sup>25</sup> Further investigation is needed to understand the interaction between sleep and anxiety states in patients injected with GLP-1RA.

Our findings highlight that GLP-1RAs not only contribute to improvements in body weight and blood sugar levels in patients with T2DM, but also positively impact dietary control and medication adherence, anxiety status and sleep quality. However, our study also had some limitations. The relatively short follow-up period may have restricted our ability to observe significant changes in self-management behaviors, anxiety, and sleep quality over time. Additionally, as a single-center study with a small sample size, the clinical characteristics, self-management behaviors, and psychological status of the patients may not represent a wider range of T2DM patients using GLP-1RAs. Admittedly, a 3-month follow-up with a single center may not provide insight into long-term self-management behaviors, anxiety, and sleep quality. Nevertheless, studies on how GLP-1 receptor agonists (GLP-1 RA) affect these factors are lacking. Future research will involve prospective multicenter studies with larger sample sizes to comprehensively assess the long-term effects of GLP-1 RA on diabetes self-management behaviors, anxiety, and sleep quality in patients with T2DM.

## Conclusion

In summary, our study is the first to reveal a significant association between GLP-1 RA and self-management behaviors, anxiety, and sleep quality in T2DM patients. This study provides valuable insights into the potential benefits of GLP-1 receptor agonists in the treatment of T2DM, particularly exploring their impact on self-management behaviors, mental state, and sleep quality, beyond traditional clinical indicators. Further long-term follow-up studies will be conducted to systematically evaluate the lasting effects of GLP-1 RA on self-management behaviors, anxiety, and sleep quality in T2DM patients.

## Data Sharing Statement

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

## Institutional Review Board Statement

This study was conducted in accordance with the Declaration of Helsinki and has received ethical approval from the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology (Mar 2020, protocol code: TJ- IRB20200315).

## Informed Consent Statement

Each participant signed written informed consent approved by the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, following the Declaration of Helsinki's principles.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflict of interest.

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