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ORIGINAL ARTICLE

Predictors of glycemic and weight responses to exenatide in patients with type 2 diabetes mellitus

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Abstract

Objective This study aimed to identify reliable predictors of haemoglobin A1c (HbA1c) reduction and weight loss within 6 months after treatment with exenatide.

Methods A total of 343 patients with type 2 diabetes mellitus were examined and followed up for 12 months. The study patients were divided into two groups: responders and non-responders, which were defined based on their glycemic control (responders: HbA1c reduction of ≥ 1.0%) and weight response (responders: weight loss of ≥ 3%) within 6 months after exenatide administration. Binary logistic regression analysis was performed to identify the predictors associated with exenatide response, and a receiver operating characteristic (ROC) curve was plotted to assess the predictive ability of the identified factors.

Results Of the 148 patients who met the inclusion criteria, 53 (35.81%) were responders and 95 (64.19%) were non-responders. Binary logistic regression analysis revealed that baseline HbA1c, baseline weight, and duration of diabetes were significant predictors of glycemic and weight responses to exenatide. The area under the curve of the ROC for the predictors of HbA1c and weight responses within 6 months after exenatide initiation was 0.765 (95% confidence interval: 0.686–0.845).

Conclusion Baseline HbA1c, baseline weight, and duration of diabetes may serve as predictors for glycemic and weight responses to exenatide.

Keywords Exenatide · Type 2 diabetes mellitus · Glycemic response · Weight response · Predictor

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterised by hyperglycaemia. Without timely intervention and treatment, it may eventually bring about life-threatening microvascular and macrovascular complications [1]. Maintaining tight glycemic control in patients with T2DM may prevent or reduce the risk of progression to some complications [2]. Until now, people have been trying to determine and maintain the appropriate glucose levels; however, nearly 50% of patients with T2DM still fail to achieve the target haemoglobin A1c (HbA1c) level of below 7%, which is extremely detrimental to the stability of the disease [3]. In addition, some patients may try to lose 5–10% of their body weight to lower their blood glucose levels, which in turn may reduce the risk of cardiovascular diseases (CVDs) to some extent [4]. However, only a few anti-hyperglycemic agents are effective in controlling weight gain [5]. Therefore, finding an appropriate anti-hyperglycemic agent is an urgent concern in clinical practice, which can not only lower HbA1c level, but also reduce weight gain.

At present, glucagon-like peptide-1 receptor agonist (GLP-1 RA) is a novel therapeutic strategy that stimulates insulin production to lower blood glucose level in a glucose-dependent manner [6]. GLP-1 RA can also indirectly play roles in various glucose regulation via the inhibition of glucagon secretion. This increases satiety which in turn

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reduces food intake and slows gastric emptying [7–10]. Clinical studies have shown that HbA1c levels and body weight were significantly reduced in patients who were administered GLP-1 RA, which is undoubtedly a good treatment option for patients with T2DM [11–13]. Yet, owing to individual differences, only 50–70% of patients had distinct therapeutic efficacy when GLP-1 RA was administered [14]. In addition, the high cost of GLP-1 RA remains a significant challenge. Physicians are aware of this issue and are cautious when prescribing GLP-1 RA to their patients. Identifying factors that can predict responses to GLP-1 RA therapy is critical in clinics as it helps physicians personalise and optimise drug utilisation in patients with T2DM with poor glycemic control.

According to the literature and our previous research, the initial high levels of HbA1c is one of the most significant predictors of the glucose-lowering effect of GLP-1 RA [15]. However, the role of weight loss in predicting the efficacy of GLP-1 RA therapy has not been fully explored. T2DM and obesity are well-known risk factors for CVDs and mortality, and substantial evidence has shown the effects of body weight reduction in preventing CVDs in patients with T2DM [16]. However, whether these factors can predict the GLP-1 RA-induced glycemic and weight responses simultaneously was not observed in patients with T2DM. Therefore, we aimed to identify the predictors of glycemic and weight responses to exenatide treatment in patients with T2DM.

Materials and methods

Study participants

Patients with T2DM admitted to in the Endocrinology Department of the Affiliated Hospital of Xuzhou Medical University in China between January 2017 and September 2019 were recruited in this retrospective study. Patients who were diagnosed with T2DM, aged > 18 years, and received exenatide treatment twice a day as part of their diabetes treatment for at least 12 months prior to data collection were included in this study. In contrast, patients who developed other subtypes of diabetes (such as type 1 diabetes and gestational diabetes), discontinued exenatide treatment within 12 months, were lost to follow-up, and were previously treated with another GLP-1 analogue were excluded.

Treatment with exenatide at a dose of 5 μg administered twice daily was initiated. After 1 month of treatment, the exenatide dosage was increased to 10 μg twice daily. The patients were followed up at 3, 6, and 12 months after treatment initiation. A total of 343 exenatide-treated patients with T2DM met the inclusion criteria. Meanwhile, 29 participants who developed adverse reactions, 101 participants who had incomplete data, and 65 participants who were lost to follow-up were excluded; hence, only 148 participants were included in the final analyses. The detailed flow chart of the participant selection process was described in our previous study [15]. The research was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University.

Measurement of the anthropometric and biochemical parameters

Data on anthropometric measurements, clinical history, and blood analyses were obtained from medical records at baseline and at each follow-up visit. Anthropometric measurements included age, weight, height, and body mass index (BMI). BMI was calculated as weight in kilograms divided by height in metres squared (kg/m^2). The duration of diabetes and use of concurrent diabetic medications were recorded. Biochemical data including HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting serum insulin (FINS), postprandial serum insulin (PINS), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were also retrieved. Insulin resistance and β-cell function were evaluated using the following formulas: homeostasis model insulin resistance assessment (HOMA-IR) = FINS (mU/L) × FPG (mmol/L)/22.5, and homeostasis model β-cell functional assessment (HOMA-B) = 20 × FINS/(FPG-3.5) [17].

Study cohorts

According to the National Institute for Health and Care Excellence guidelines regarding the use of GLP-1 RA in the treatment of patients with T2DM, glycemic response was defined as an HbA1c reduction of ≥ 1.0% and weight responses as a weight loss of ≥ 3% within 6 months after GLP-1 RA treatment [18, 19]. Therefore, patients with T2DM were categorised into two cohorts in terms of glycemic and weight responses to exenatide: responders and non-responders. Responders were defined as patients who achieved an HbA1c reduction of ≥ 1% and a weight loss of ≥ 3%, whereas non-responders referred to patients who failed to achieve these decreases within 6 months after exenatide administration.

Statistical analysis

Statistical analyses were performed using SPSS software (version 13.0 for Windows; SPSS Inc., Chicago, IL, USA). Variables with a normal distribution were expressed as mean ± standard error, while those with a non-normal distribution are expressed as median (interquartile range) or percentages as appropriate. The baseline characteristics

between responders and non-responders were compared using the independent Student's *t*-test for continuous data and the chi-square test or Fisher's exact test for categorical data. Repeated measures analysis of variance was used to determine changes in clinical parameters at certain time points for responders group and non-responders group. Linear regression was utilised to evaluate the relationship between weight change from baseline and HbA1c change from baseline after 6 months of exenatide therapy, while binary logistic regression analysis was utilised to identify the independent predictors of glycemic and weight responses to exenatide. The odds ratio (OR) values were presented along with 95% confidence intervals (CIs). The area under the curve (AUC) of the receiver operating characteristic (ROC) curve and the 95% CI were calculated to compare the predictive power of the predictors. A p value of < 0.05 was considered significant.

Results

Patient disposition and baseline characteristics

Patient selection and disposition for the individual studies were described previously [15]. The final analysis included 148 patients (90 men and 58 women), who were divided into responders and non-responders. Of the 148 patients, 53 were responders (35.81%) and 95 were non-responders (64.19%). After 6 months of exenatide treatment, only 35.81% of the patients with T2DM achieved the composite end point (HbA1c reduction of $\geq 1\%$ and weight loss of $\geq 3\%$). The baseline characteristics of the patients are summarised in Table 1. Patients in the responder group had higher mean values for HbA1c ($p < 0.05$), weight ($p < 0.001$), and BMI ($p < 0.01$) but had a lower mean value for duration of diabetes ($p < 0.001$) than those in the non-responder group.

Effects of exenatide on clinical parameters at each time point

Supplementary material Tables S1 show the changes in clinical parameters from baseline to 12 months after exenatide treatment by repeated measures ANOVA on clinical data. Exenatide treatment led to significant improvements in HbA1c, body weight, BMI, FPG, PPG, HOMA-IR, HOMA-B, and blood lipids levels in each group. Furthermore, the clinical parameters were also compared between responders and non-responders. The baseline HbA1c level was higher among responders, while the HbA1c levels at 3, 6, and 12 months were higher among non-responders (Fig. 1A). Weight was, on average, greater in responders than in non-responders during the entire study period (Fig. 1B). The BMI at baseline was greater in responders than in non-responders (Fig. 1C). The patterns of FPG and PPG changes were similar between responders and non-responders (Fig. 1D, E). In addition, no significant difference was observed between the two groups in terms of HOMA-B at baseline and 3 months; in contrast, the responders had higher levels of HOMA-B at 6 months and 12 months than the non-responders (Fig. 1F).

Table 1 Comparison of baseline characteristics between responders ($n = 53$) and non-responders ($n = 95$) in patients with T2DM after exenatide initiation

Parameters	Group		p value
	Responders	Non-responders	
N (male/female)	53 (34/19)	95 (56/39)	0.534
Age (years)	47.92 ± 1.30	50.03 ± 0.91	0.180
HbA1c (%)	9.51 ± 0.20	8.98 ± 0.11	0.033
Weight (kg)	89.31 ± 1.73	82.12 ± 1.26	<0.001
BMI (kg/m^2)	30.88 ± 0.59	28.82 ± 0.34	0.006
Duration of diabetes (years)	1.57 ± 0.35	5.09 ± 0.57	<0.001
Exenatide only (%)	11 (20.75)	21 (22.11)	0.848
Exenatide + OHAs (%)	21 (39.62)	32 (33.68)	0.470
Exenatide+ insulin (%)	8 (15.09)	14 (14.74)	0.953
Exenatide+ OHAs + insulin (%)	13 (24.53)	28 (29.47)	0.519

Data are provided as mean ± standard error or percentages unless otherwise noted

HbA1c haemoglobin A1c, *BMI* body mass index, *OHA* oral anti-hyperglycemic agent

Predictors of glycemic and weight responses within 6 months after exenatide initiation

Linear regression analysis was used to assess the possible predictors of glycemic and weight responses within 6 months after exenatide initiation. Baseline HbA1c (OR = 1.664, CI: 1.059–2.616, $p = 0.027$), baseline weight (OR = 1.064, CI: 1.022–1.109, $p = 0.003$), and duration of diabetes (OR = 0.757, CI: 0.647–0.886, $p = 0.001$) were independent predictors of response to exenatide treatment (Table 2). Patients with a higher baseline HbA1c, a higher baseline weight, and a shorter duration of diabetes were more likely to be classified as responders to exenatide. Furthermore, the association between changes in HbA1c level and weight, which were closely related to the response to exenatide within 6 months after treatment, was further investigated using linear regression analysis. The results showed that the variation in weight was consistent with that of HbA1c level (Fig. 2). That is to say, as the weight loss increased, the HbA1c reduction also increased, which may have strengthened the glycemic and weight control within the 6-month period.

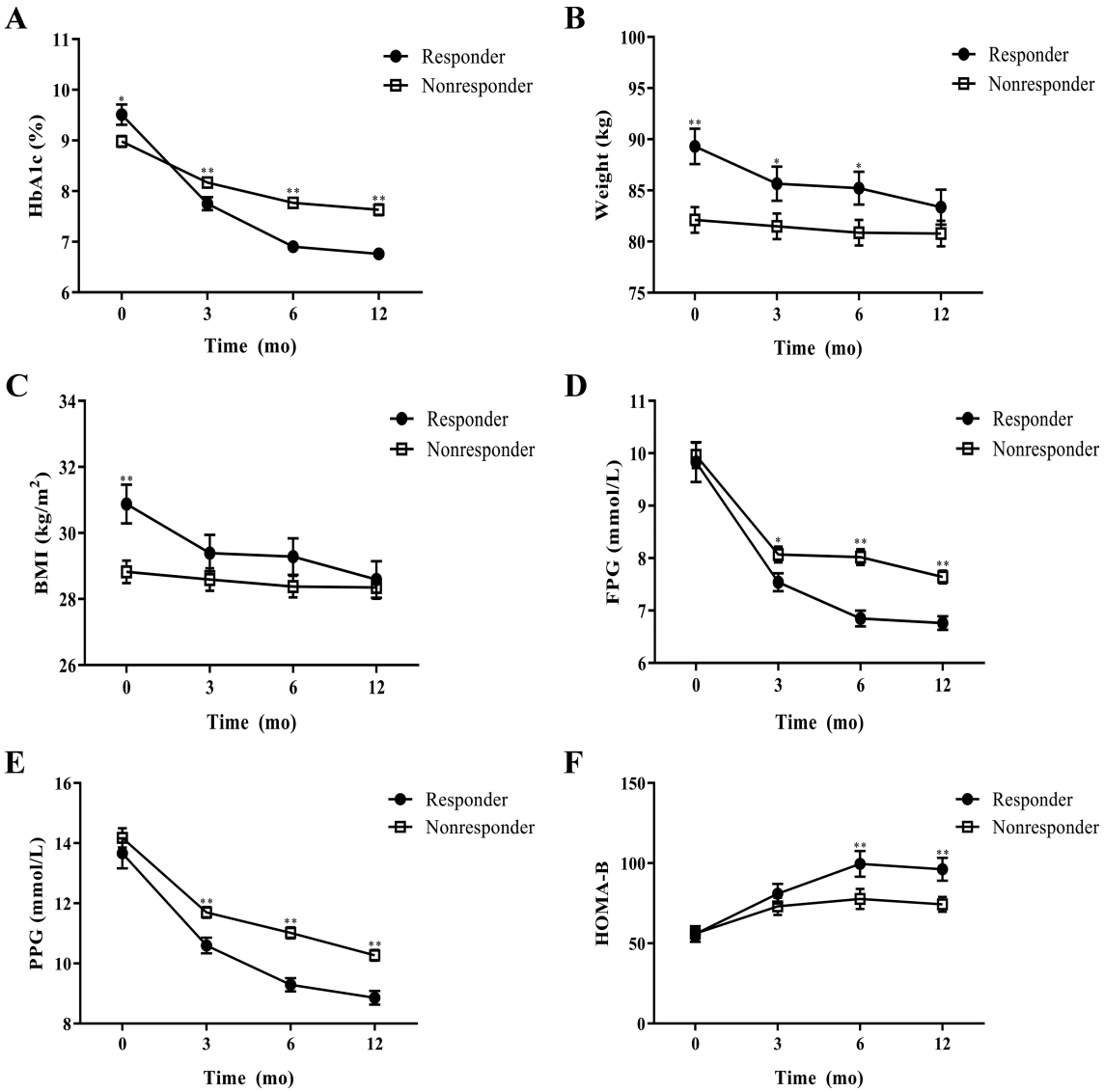

Fig. 1 Comparison of HbA1c (**A**), weight (**B**), BMI (**C**), FPG (**D**), PPG (**E**), and HOMA-B (**F**) between responders (n = 53) and non-responders (n = 95) after treatment with exenatide at baseline, 3 months, 6 months, and 12 months. *$p < 0.05$, **$p < 0.01$ compared with non-responders. Abbreviations: HbA1c, haemoglobin A1c; BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HOMA-B, homeostasis model assessment for beta cell function

ROC curves for the predictors of response to exenatide

The ROC curves of the response to exenatide for HbA1c, weight, and duration of diabetes are shown in Fig. 3. The area under the ROC curve for the predictors of HbA1c and weight reduction within 6 months of exenatide initiation was 0.765 (95% CI: 0.686–0.845). Furthermore, the area under the ROC curve was used to determine the extent of the predictors of response to exenatide therapy (Supplementary material Fig. S1). The areas under the ROC curves were 0.704 (95% CI: 0.621–0.787) for diabetes duration, 0.667 (95% CI: 0.576–0.757) for baseline weight, and 0.606 (95% CI: 0.500–0.712) for baseline HbA1c. However, no significant difference was observed in the AUC for all three predictors ($p \geq 0.05$).

Discussion

Findings from the present study confirmed the potential predictors of glycemic and weight responses to exenatide in patients with T2DM. Our data showed that baseline HbA1c, baseline weight, and duration of diabetes were independent predictors of response to exenatide treatment. Patients with higher baseline HbA1c, higher baseline weight, and shorter

Table 2 Binary logistic regression analysis of the potential variables for predicting response on HbA1c level and weight changes

Variables	Odds Ratio	95% CI	*p* value
Age (years)	1.020	0.968-1.075	0.454
Sex[a]	1.396	0.529-3.679	0.500
Duration of diabetes (years)	0.757	0.647-0.886	0.001
Baseline Weight (kg/m^2)	1.064	1.022-1.109	0.003
Baseline HbA1c (%)	1.664	1.059-2.616	0.027
Baseline FPG (mmol/L)	1.048	0.761-1.443	0.773
Baseline PPG (mmol/L)	0.815	0.627-1.060	0.127
Baseline FINS (mU/L)	0.963	0.904-1.026	0.246
Baseline PINS (mU/L)	1.004	0.984-1.024	0.720
Baseline TC (mmol/L)	0.845	0.450-1.584	0.599
Baseline TG (mmol/L)	0.779	0.523-1.159	0.217
Baseline HDL-C (mmol/L)	1.610	0.235-11.050	0.628
Baseline LDL-C (mmol/L)	0.816	0.436-1.528	0.526
OHA only[b]	1.955	0.644-5.931	0.237
Insulin only[b]	1.873	0.444-7.896	0.393
OHAs and Insulin[b]	0.864	0.242-3.081	0.822

BMI, body mass index; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FINS, fasting serum insulin; PINS, postprandial serum insulin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OHA, oral anti-hyperglycemic agent; CI, confidence interval

[a]Denotes a variable that was compared against males

[b]Denotes a variable that was compared against exenatide as a monotherapy

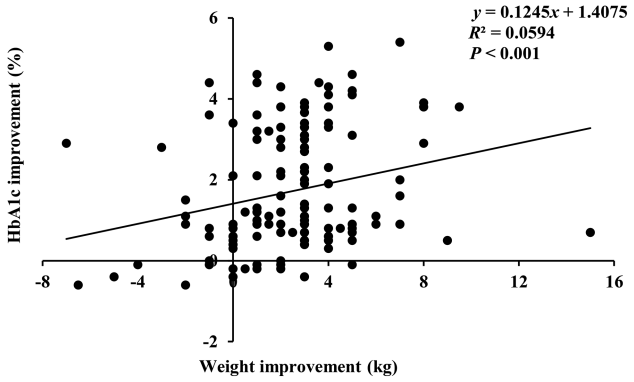

Fig. 2 Linear relationship between weight change from baseline and HbA1c change from baseline after 6 months of exenatide therapy. Results were shown using the equation for the line of best fit. Abbreviation: HbA1c, haemoglobin A1c

duration of diabetes may be more responsive to exenatide treatment, which suggests that these factors can be valuable for predicting the effect of exenatide therapy.

Accumulating evidence has reported that exenatide improved not only glycemic control, but also weight loss

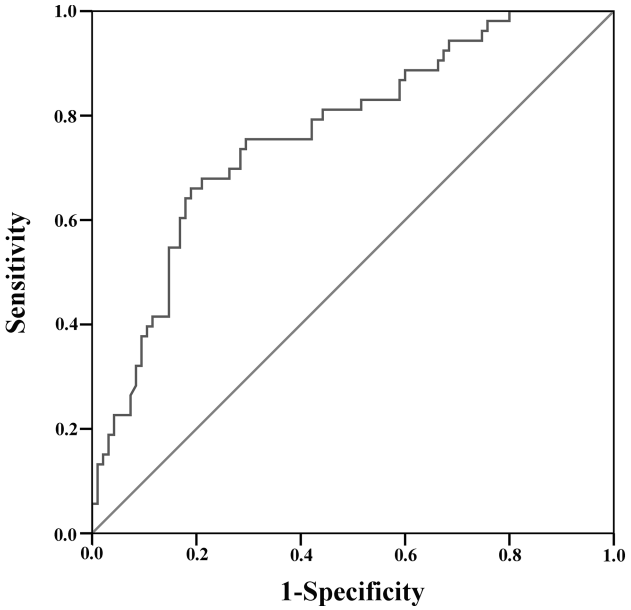

Fig. 3 ROC curve for the predictors of glycemic and weight responses to exenatide in patients with T2DM

[20, 21]. However, only 35.81% of the study patients treated with exenatide for 6 months achieved an HbA1c reduction of ≥ 1% and a weight loss of ≥ 3%. Based on the marked interindividual differences in therapeutic response of patients with T2DM treated with exenatide, further studies are needed to identify the novel predictors for individualised treatment [22]. To the best of our knowledge, this study was the first to identify the factors that can predict the glycemic and weight responses to exenatide simultaneously in patients with T2DM. The predictors of glycemic and weight responses are baseline HbA1c, baseline weight, and duration of diabetes in patients on exenatide therapy. Several studies have reported that the baseline HbA1c level appears to be an independent predictor of glycemic response to exenatide, as observed in our previous studies [11, 15, 18]. In a 24-month retrospective study of once-weekly exenatide in Spain, HbA1c was found to be a unique independent predictor of glycemic response; higher BMI and previous treatment with DPP-4i could also predict weight response [11, 15]. However, these studies did not agree with our results. Furthermore, these inconsistencies are likely due to the different grouping schemes and timing of subcutaneous injections.

The reason that patients gradually lose weight after taking exenatide may be delayed gastric emptying and enhanced satiety induced by the hypothalamus which control caloric intake [23, 24]. Additionally, the responder group had a more significant trend in weight loss with a higher baseline BMI, which was broadly in line with previous findings [25, 26]. These data provided strong evidence to allay the physicians' concerns that exenatide-treated

patients with T2DM may experience excessive weight loss when compared with the upper baseline weight. Futhermore, patients with a history of ≥ 5 years of diabetes were less likely to achieve good glycemic control than those with a history of < 5 years of diabetes [27]. Another drug for GLP-1 RA, liraglutide, was also more effective in patients with a shorter duration of diabetes [28]. However, it is important to note that the risk of hypoglycemia increases by 19% per decade of duration on the premise of longer duration of diabetes, meaning that without intervention, patients could be subjected to lifelong insulin therapy [29]. Hence, the duration of diabetes was considered a valuable predictor of response to exenatide treatment.

With regard to the discriminatory powers of predictive ability, our ROC curve analysis showed that the AUC was attributed to predicting HbA1c and weight reduction within 6 months after exenatide treatment. The AUC values for the duration of diabetes, baseline weight, and baseline HbA1c were 0.704, 0.667 and 0.606, respectively. Although many studies have evaluated the predictors of response to exenatide, only a few have attempted to plot an ROC curve to assess the predictive ability of these factors, which were identified by binary logistic regression analysis [11, 14, 15, 18, 21]. To date, only one study found that the mean preprandial blood glucose level had the highest AUC (0.72) for the prediction of glycemic response to GLP-1 RA, and the results of this study were similar to those of our study [30].

Although we have identified the predictive factors, there are still some inherent problems in this study that need to be improved. First, owing to the number of patients who did not meet the inclusion criteria, the number of patients included for the final analysis was small, resulting in a wide range in CI after the analysis. It is necessary to expand the sample size; in this case, other races can also be included to increase the richness of the samples, and the generalisability of the results could be determined subsequently. Furthermore, after exenatide administration, if the patients had other treatments or strictly controlled diet and rest, it would have been difficult to clearly judge whether the significant decreases in HbA1c levels and body weight were simply a direct effect of exenatide. This suggests that we should pay attention to changes in medication categories and lifestyles during patient follow-up and assess their impact on the efficacy of exenatide. Finally, this study only tentatively identified baseline HbA1c, baseline weight, and duration of diabetes as predictors of responses to exenatide and their relationships to other indicators. However, the scopes of the three predictors have not been further refined; thus the clinical reference of the results could not be highlighted. The determination of the applicable scopes of predictors still requires the support of a larger sample size. Therefore, a prospective clinical study with a stricter protocol and a greater number of patients using each formulation is necessary to further evaluate the effectiveness of GLP-1 RA therapy.

Conclusion

Baseline HbA1c, baseline weight, and duration of diabetes could be independently used to predict glycemic and weight responses to exenatide in patients with T2DM. The scopes of each indicator has not been determined; thus, further explorations are needed to provide more valuable references for the applicable conditions of exenatide and selections for patients with T2DM. Significant predictors of exenatide and reliable clinical data can contribute to individualised treatment, which is more conducive to achieving better glycemic and weight gain control in patients with T2DM.

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Authors Contribution Yuhan Huang: Conceptualization, Methodology, Writing-Original Draft, Writing-Reviewing and Editing. Yanan Yu: Formal Analysis, Methodology, Data Curation, Investigation. Ruonan Hu: Data Curation, Validation, Writing-Editing. Ke Xu: Data curation, Writing-Editing. Tao Wang: Methodology, Resources, Supervision, Funding Acquisition, Project Administration, Writing-Reviewing and Editing. Hongwei Ling: Data Curation, Investigation, Supervision. Jia Han: Data Curation, Methodology, Investigation. Dongmei Lv: Resources, Conceptualization, Supervision, Project Administration.

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Data availability The data underlying this article are available in the article and its online supplemental material.

Declarations

Ethical approval The study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Xuzhou, China) and was performed in accordance with the Declaration of Helsinki. The ethical approval number was XYFY 2018-KL085 on 31 December 2018.

Conflicts of interest The authors declared no other competing financial interests or disclosures relevant to this manuscript exist for all authors.

Consent of participation Written informed consent was obtained from all participants prior to enrollment.

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