Analysis of the effect of liraglutide on glycemic variability in patients with type 2 diabetes

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Abstract. The efficacy of liraglutide in the treatment of glycemic variability in type 2 diabetic patients remains to be fully elucidated. Some studies evaluated the efficacy and safety of liraglutide in glycemic variability, and this meta-analysis was performed to evaluate the accuracy of the results of existing studies on the efficacy of liraglutide. We conducted a comprehensive search for all relevant studies published in PubMed, EMBASE, Cochrane Library, and China Academic Journal Full-Text Database from the beginning of 2011 to October 31, 2019. The mean ± SD and 95% confidence interval were used for evaluation, and subgroup and sensitivity analysis were carried out. Publication bias was estimated by funnel plots and Egger’s tests. A total of 16 studies were included in the meta-analysis involving 492 participants. MAGE (mean amplitude of glycemic excursion), LAGE (largest amplitude of glycemic excursions), SD (standard deviation of blood glucose), and MODD (mean of daily differences) were collected to reflect the variability of blood glucose. The glycemic variability indexes of patients before and after treatment with liraglutide were compared. Patients with treatment had lower glycemic variability compared with patients receiving treatment of liraglutide. Compared with the patients before the treatment, the patients after the treatment had a smaller glycemic variability (MAGE: $\bar{F} = 92\%, p < 0.01, Z = 11.91, p < 0.01$, $MD = -2.78, 95\% CI: -3.24 - -2.32$; LAGE: $\bar{F} = 76\%, p = 0.08, Z = 9.94, p < 0.01, MD = -2.20, 95\% CI: -2.59 - -1.81$; MODD: $\bar{F} = 74\%, p = 0.002, Z = 14.03, p < 0.01, MD = -0.90, 95\% CI: -1.02 - -0.77$; SD: $\bar{F} = 93\%, p < 0.01, Z = 3.62, p < 0.01, SMD = -1.77, 95\% CI: -2.73 - -0.81$). Sensitivity analysis showed that our results were reliable and no evidence of significant publication bias was detected. The results of this study suggest that patients with type 2 diabetes treated with liraglutide are associated with lower glycemic variability.

Key words: Liraglutide, Glycemic variability, Type 2 diabetes, Meta-analysis

CURRENTLY, TYPE 2 DIABETES (T2DM) is a common metabolic disease with increasing prevalence worldwide [1]. In general, glycemic control is based on the measurement of glycated hemoglobin (HbA1c). However, this indicator does not accurately reflect glycemic variability. Patients with type 2 diabetes mellitus may still show a significant increase in glycemic variability despite achieving target control of HbA1c [2]. Glycemic variability, a pattern of blood glucose disorders, is a key risk factor for diabetic complications [3]. And it can be simply defined as the degree to which a patient’s blood glucose level fluctuates between high (peak) and low (minimum) levels [4]. In the current study, blood glucose was assessed for variability by MAGE, LAGE, MODD, and SD [3]. Conventional drugs for type 2 diabetes do not effectively control hyperglycemia, and the frequently occurring side effects remain a major problem waiting to be solved [5]. One treatment for reducing glycemic variability and persistent hyperglycemia is the treatment with glucagon-like peptide-1 receptor agonist (GLP-1RA) [6]. Liraglutide is a kind of glucagon like peptide-1 receptor agonist with pharmacokinetic properties, which is suitable for once a day administration in patients with type 2 diabetes [7]. Subcutaneous injection of liraglutide has been approved in several countries for the treatment of patients with type 2 diabetes, including the United States and Europe [8]. Kim et al. analyzed the results of 15 studies showing that GLP-1RA significantly reduced HbA1c [9]. Currently, there is a lack of studies on the effect of liraglutide on glycemic variability. This article aims to provide an objective basis for the clinical application of liraglutide in improving blood glycemic...
variability in patients with type 2 diabetes, and hopes to explore new treatment methods in the future.

Materials and Methods

Literature Search Strategy
Liraglutide, diabetes mellitus, and the related indicators of glycemic variability were used as subject words and key words for joint retrieval. All relevant documents published before October 31, 2019 were searched for in detail in PubMed, EMBASE, Cochrane Library, and China Academic Journal Full-Text Database (CNKI).

Inclusion criteria
The inclusion criteria were as follows: (1) the studies were related to the efficacy of patients with type 2 diabetes treated with liraglutide; (2) studies were related to the relationship between liraglutide and glycemic variability, and provide the exact sample size, and the mean and standard deviation of the indicators related to glycemic variability; (3) the diagnosis of diabetes was clear [10]; (4) there was no direct correlation between the studies.

Exclusion Criteria
The exclusion criteria were as follows: (1) the data of literature were incomplete or with too little information, and the extraction of the original data was not sufficient to calculate the statistics of the study; (2) case reports and observation studies were without comparison of pre-treatment and post-treatment; (3) there was no data on glycemic variability before and after treatment with liraglutide; (4) the subset of articles published by the same author or articles were published repeatedly; (5) research was limited to animals.

Study Selection
Two researchers independently screened the literature, extracted the data, and cross-checked their results. If the results were inconsistent, they would be discussed together by the two researchers or evaluated by a third senior researcher. In this study, pre-established data extraction forms were used to extract data from the literature that was finally included in the meta-analysis. The extract content included the first author, year of publication, study area, sample size, mean ± standard deviation of related indicators of blood glycemic variability.

Statistical Analysis
According to the requirements of the meta-analysis, the data were compiled, the database was established, and the data were carefully checked. RevMan5.3 analysis software was used for statistical analysis, mean difference and 95% confidence interval (95%CI) were used for quantitative analysis of measurement data. $F$ was used to test the heterogeneity among the studies. If $F \leq 50\%$, the heterogeneity was considered not statistically significant, and the fixed effect model was used for analysis. Otherwise, if $F > 50\%$, the heterogeneity was considered statistically significant, and the random effect model was used for analysis. The source of heterogeneity was explored, and a subgroup analysis was conducted based on the factors that may produce heterogeneity. Sensitivity analysis was performed to ensure the stability of the results of the meta-analysis. The included studies were removed one by one, and the combined analysis was re-analyzed to compare whether there was a significant difference between the effect values before and after the combination. Funnel plots and Egger’s test were used to evaluate publication bias. If $p < 0.05$ it was considered statistically significant, suggesting that publication bias was not excluded. If the number of studies included was less than 10, the stability of the conclusions were further evaluated after eliminating the publication bias with trim and fill method.

Results

Literature search results
Upward of one hundred relevant studies were preliminarily retrieved through keywords, and 16 studies finally met the predetermined inclusion and exclusion criteria. These 16 studies evaluated the changes in glycemic variability among participants before and after treatment with liraglutide (Fig. 1). The data from these studies showed statistically significant differences in glycemic variability between type 2 diabetic patients receiving liraglutide and type 2 diabetes patients who did not receive liraglutide. The relevant literature was published from 2011 to 2019 (Table 1). A total of 492 patients with type 2 diabetes were included in the literature. The indicators of glycemic variability in 13 studies were obtained from CGM. Indicators of glycemic variability in the three other studies did not indicate source. The information on the concomitant medication or injections and the dose of liraglutide is shown in Table 2.

Results of Meta-analysis

Effect on MAGE in patients with type 2 diabetes
Sixteen articles were related to the comparison of MAGE of type 2 diabetic patients before and after treatment with liraglutide. A total of 492 patients with type 2 diabetes were included. The results of the analysis showed that the effect of liraglutide on MAGE in patients with type 2 diabetes was significantly different from that before treatment with liraglutide ($F = 92\%, p <$
0.01, \( Z = 11.91, p < 0.01, MD = \text{–}2.78, 95\% CI: \text{–}3.24 – \text{–}2.32; \text{ Fig. 2}. \) Therefore, liraglutide has a stronger reduction effect on MAGE. Egger’s test \((p = 0.376)\) indicated that there was no obvious publication bias. Funnel plot is shown in Fig. 3.

**Effect on LAGE in patients with type 2 diabetes**

Six studies involving 169 patients with type 2 diabetes compared LAGE in patients with type 2 diabetes before and after treatment with liraglutide. The meta-analysis showed that the LAGE of patients with type 2 diabetes after treatment with liraglutide was significantly different from that before treatment \((I^2 = 76\%, p = 0.08, Z = 9.94, p < 0.01, MD = 4.83, 95\% CI: \text{–}5.78 – \text{–}3.87; \text{ Fig. 4}). \) Therefore, liraglutide has a greater effect on the reduction of LAGE than that without treatment with liraglutide. Egger’s test \((p = 0.500)\) indicated no significant publication bias. Funnel plot is shown in Fig. 5.

**Effect of MODD on type 2 diabetes patients**

Six studies involving 237 patients compared MODD in patients with type 2 diabetes before and after treatment with liraglutide. Meta-analysis showed that the effect of liraglutide on MODD in patients with type 2 diabetes was significantly different from that before treatment \((I^2 = 74\%, p = 0.002, Z = 14.03, p < 0.01, MD = \text{–}0.90, 95\% CI: \text{–}1.02 – \text{–}0.77; \text{ Fig. 6}). \) Therefore, liraglutide had a greater effect on reducing MODD. Egger’s test \((p = 0.02)\) indicated there was publication bias in the analysis. However, further analysis of the trim and fill method showed that the publication bias does not affect the estimator, and it is more certain that the effect size estimate obtained in the meta-analysis is valid. The funnel plot is shown in Fig. 7.

**Effect on SD in patients with type 2 diabetes**

Six studies involving 237 patients compared SD in patients with type 2 diabetes before and after treatment with liraglutide. Meta-analysis showed that the effect of liraglutide on SD in patients with type 2 diabetes was significantly different from that before treatment with liraglutide \((I^2 = 93\%, p < 0.01, Z = 3.62, p < 0.01, SMD = \text{–}1.77, 95\% CI: \text{–}2.61 – \text{–}0.81; \text{ Fig. 8}). \) Therefore, liraglutide had a stronger effect on reducing SD. Egger’s test \((p = 0.991)\) indicated no significant publication bias. The funnel plot is shown in Fig. 9.

**Subgroup analysis**

Due to the heterogeneity of the 16 studies included, in order to further increase the reliability of the study, a subgroup analysis of HbA1c and age in diabetic patients was performed.

**MAGE:** a. HbA1c: according to the level of HbA1c, patients were divided into two subgroups: HbA1c ≥ 9% and HbA1c < 9%. There were eight studies that involved 386 patients with type 2 diabetes with HbA1c < 9% \((I^2 = 70\%, p < 0.01, Z = 14.69, p < 0.01, WMD = \text{–}2.30, 95\% CI: \text{–}2.61 – \text{–}2.00)\), and the difference was statistically significant. There were seven studies involving 170 patients with type 2 diabetes mellitus with HbA1c ≥ 9%
### Table 1  Basic characteristics of the included studies

| Author          | Year | country | MAGE | After treatment | Before treatment |
|-----------------|------|---------|------|----------------|-----------------|
| Author          | Year | country | Mean | SD  | n  | Mean | SD  | n  |
| Donghua Yu [10] | 2016  | China   | 3.6  | 1.4 | 20 | 7.4  | 2.4 | 20 |
| Guanghui L [11] | 2017  | China   | 1.42 | 0.45| 37 | 3.99 | 1.48| 37 |
| Jiaming Wu [12] | 2016  | China   | 4.9  | 1.1 | 30 | 6.5  | 1.1 | 30 |
| Ma, Z [13]      | 2015  | China   | 3.6  | 1.3 | 31 | 5.22 | 1.56| 31 |
| Qian Huang [14] | 2018  | China   | 3.7  | 1.5 | 20 | 11.3 | 2.7 | 20 |
| Shufang Yu [15] | 2019  | China   | 3.47 | 0.38| 45 | 7.58 | 1.47| 45 |
| Yan, L [16]     | 2015  | China   | 3.18 | 1.03| 25 | 4.2  | 2.19| 25 |
| Yingbo Yang [17]| 2017  | China   | 1.53 | 0.46| 40 | 3.89 | 0.58| 40 |
| Zhaosui Huang [18]| 2016 | China   | 3.2  | 1.7 | 28 | 7.6  | 4.1 | 28 |
| Jie Zhang [19]  | 2014  | China   | 1.52 | 0.27| 40 | 3.98 | 0.52| 40 |
| Xiaoxia Fan [20]| 2018  | China   | 2.53 | 1.43| 42 | 5.42 | 1.82| 42 |
| Tianying Yu [21]| 2019  | China   | 1.81 | 0.36| 10 | 3.96 | 0.52| 10 |
| Taniguchi, Y [22]| 2011 | Japan   | 2.68 | 1.68| 80 | 4.55 | 2.06| 80 |
| Mori, Y [23]    | 2011  | Japan   | 2.22 | 1.27| 20 | 7.5  | 2.5 | 20 |
| Levit, S [24]   | 2018  | Israel  | 3.6  | 1.3 | 18 | 4.61 | 1.81| 18 |
| Funakoshi, S [25]| 2015 | Japan   | 3.78 | 1.22| 6  | 6.72 | 1.72| 6  |

| Author          | Year | country | LAGE | After treatment | Before treatment |
|-----------------|------|---------|------|----------------|-----------------|
| Author          | Year | country | Mean | SD  | n  | Mean | SD  | n  |
| Donghua Yu [10] | 2016  | China   | 7.2  | 1.9 | 20 | 12.8 | 2.9 | 20 |
| Ma, Z [13]      | 2015  | China   | 7.3  | 2.1 | 31 | 13.1 | 3.4 | 31 |
| Qian Huang [14] | 2018  | China   | 7.3  | 1.8 | 20 | 12.9 | 2.8 | 20 |
| Shufang Yu [15] | 2019  | China   | 7.53 | 1.18| 45 | 12.38| 2.17| 45 |
| Yan, L [16]     | 2015  | China   | 2.34 | 0.57| 25 | 5.42 | 1.82| 42 |
| Zhaosui Huang [18]| 2016 | China   | 7.4  | 1.3 | 28 | 12.3 | 2.5 | 28 |

| Author          | Year | country | MODD | After treatment | Before treatment |
|-----------------|------|---------|------|----------------|-----------------|
| Author          | Year | country | Mean | SD  | n  | Mean | SD  | n  |
| Donghua Yu [10] | 2016  | China   | 1.3  | 0.7 | 20 | 2.4  | 0.9 | 20 |
| Guanghui Li [11]| 2017  | China   | 0.38 | 0.25| 37 | 1.57 | 0.41| 37 |
| Qian Huang [14] | 2018  | China   | 1.4  | 0.6 | 20 | 2.6  | 0.2 | 20 |
| Yingbo Yang [17]| 2014  | China   | 0.43 | 0.29| 40 | 1.28 | 0.44| 40 |
| Jie Zhang [19]  | 2018  | China   | 0.45 | 0.13| 40 | 1.29 | 0.34| 40 |
| Tianying Yu [21]| 2019  | China   | 0.76 | 0.2 | 80 | 1.49 | 0.26| 80 |

| Author          | Year | country | SD  | After treatment | Before treatment |
|-----------------|------|---------|------|----------------|-----------------|
| Author          | Year | country | SD  | Mean | SD  | n  | Mean | SD  | n  |
| Jiaming Wu [10] | 2016  | China   | 2.2  | 0.2 | 30 | 2.8  | 0.3 | 30 |
| Shufang Yu [15] | 2019  | China   | 1.28 | 0.2 | 45 | 3.18 | 0.47| 45 |
| Zhaosui Huang [18]| 2016| China   | 1.3  | 1  | 28 | 3.1  | 2.2 | 28 |
| Xiaoxia Fan [20]| 2018  | China   | 1.21 | 0.32| 42 | 2.61 | 1.31| 42 |
| Taniguchi, Y [22]| 2011 | Japan   | 1.01 | 0.66| 10 | 1.96 | 0.83| 10 |
| Mori, Y [23]    | 2011  | Japan   | 1.722| 0.61| 20 | 2.11 | 0.61| 20 |
| Levit, S [24]   | 2018  | Israel  | 1.75 | 0.63| 18 | 2.7  | 1.02| 18 |
\( I^2 = 96\% , p < 0.01 , Z = 5.55 , p < 0.01 , \text{WMD} = -3.57 , 95\% \text{CI}: -4.83 \text{ to } -2.31 \), and the difference was statistically significant. This analysis indicated that there was a correlation between treatment with liraglutide and the smaller MAGE in patients with type 2 diabetes with HbA1c \( \geq 9\% \) (Fig. 10). b. Age: according to the average age of patients with type 2 diabetes mellitus, the patients were divided into three subgroups: ages between 40–50, ages between 50–60 and ages >60. There were four studies involving 123 patients with type 2 diabetes with an average age of 40–50 years. The result of heterogeneity test was \( I^2 = 94\% , p < 0.01 , Z = 4.26 , p < 0.01 , \text{WMD} = -3.42 , 95\% \text{CI}: -4.99 \text{ to } -1.84 \), and the difference was statistically significant. Seven studies involved 202 patients with type 2 diabetes with an average age of 50–60 years. The results of heterogeneity test were \( I^2 = 94\% , p < 0.01 , Z = 6.49 , p < 0.01 , \text{WMD} = -3.13 , 95\% \text{CI}: -4.08 \text{ to } -2.19 \), and the difference was statistically significant. The four studies involved 161 patients with type 2 diabetes with an average age over 60 years. The results of heterogeneity test were \( I^2 = 47\% , p = 0.13 , Z = 4.06 , p < 0.01 , \text{WMD} = -2.12 , 95\% \text{CI}: -2.41 \text{ to } -1.82 \), and the difference was not statistically significant (Fig. 11). It was suggested that the treatment with liraglutide in type

**Table 2** The information of the concomitant medication or injections and dose of liraglutide

| Author          | Liraglutide (mg/d) | Concomitant medication |
|-----------------|--------------------|------------------------|
| Donghua Yu      | NA                 | Insulin                |
| Guanghui L      | 0.6–1.0–1.2        | Insulin + OADS         |
| Jiaming Wu      | 0.6–1.2 (<1.8)     | OADS                   |
| Ma, Z           | 0.6–1.2 (<1.8)     | OADS                   |
| Qian Huang      | NA                 | Insulin                |
| Shufang Yu      | 0.6–1.2 (<1.8)     | NA                     |
| Yan, L          | 0.6–1.2            | OADS                   |
| Yingbo Yang     | 0.6–1.2            | Insulin + OADS         |
| Zhaozui Huang   | 0.6–1.2 (<1.8)     | OADS                   |
| Jie Zhang       | 0.6–1.2            | Insulin + OADS         |
| Xiaoxia Fan     | 0.6–1.2 (<1.8)     | OADS                   |
| Tianying Yu     | 0.9                | OADS                   |
| Taniguchi, Y    | 0.6–1.2            | NA                     |
| Mori, Y         | 0.9                | OADS                   |
| Levit, S        | NA                 | Insulin + OADS         |
| Funakoshi, S    | NA                 | Insulin                |

Note: 0.6–1.2: the first week’s dose is 0.6 mg/d, the maintenance dose is 1.2 mg/d; 0.6–1.2 (<1.8): the first week’s dose is 0.6 mg/d, the maintenance dose is 1.2 mg/d. It can be added to 1.8 mg/d if necessary. NA: not available.
2 diabetic patients with an average age of 40-60 years was related to the smaller MAGE, while the treatment with liraglutide in type 2 diabetic patients with an average age of more than 60 years was not related to the smaller MAGE.

LAGE: according to the level of HbA1C, patients were divided into two subgroups: HbA1C ≥ 10% and HbA1C < 10%. There were four studies involving 113 type 2 diabetic patients with HbA1C < 10%. The results were $F = 0\%$, $p = 0.70$, $Z = 19.12$, $p < 0.01$, WMD = −5.04, 95%CI: −5.56 − −4.53, and the difference was not statistically significant. Two studies involved 56 patients with type 2 diabetes mellitus with HbA1c ≥ 10%. The results were $F = 92\%$, $p < 0.01$, $Z = 2.67$, $p < 0.01$, WMD = −4.19, 95%CI: −7.27 − −1.11, and the difference was statistically significant (Fig. 12). The results indicate that patients with type 2 diabetes with HbA1C ≥ 10% who received treatment with liraglutide were associated with smaller LAGE. Patients with type 2 diabetes with HbA1C < 10% were not associated with smaller LAGE when treated with liraglutide.

MODD: a. HbA1C: according to the level of HbA1C, patients were divided into two subgroups: HbA1C ≥ 9% and HbA1C < 9%. There are three studies involving 117 patients with type 2 diabetes with HbA1C less than 9%. The results were $F = 22\%$, $p = 0.28$, $Z = 18.96$, $p < 0.01$, WMD = −0.89, 95%CI: −0.98 − −0.79, and the difference was not statistically significant. Three studies involved 120 patients with type 2 diabetes with HbA1C ≥ 9%. The results were $F = 83\%$, $p < 0.01$, $Z = 5.22$, $p < 0.01$, WMD = −0.98, 95%CI: −1.35 − −0.61, and the difference was statistically significant (Fig. 13). It is suggested that in type 2 diabetic patients with HbA1C < 9%, there was no correlation between treatment with liraglutide and smaller MODD. In type 2 diabetic patients with HbA1c ≥ 9%, the treatment with liraglutide was associated with a smaller MODD. b. Age: Patients were divided into two subgroups according to whether their ages were greater than 60 years old. Four studies involved 117 patients with type 2 diabetes with an average age less than 60 years. The results of heterogeneity test were $F = 58\%$, $p < 0.01$, $Z = 12.10$, $p < 0.01$, WMD = −0.98, 95%CI: −1.14 − −0.82, and the difference was statistically significant. Two studies involved 120 patients with type 2 diabetes with an average age of 60 years or older. The result of heterogeneity test was $F = 42\%$, $p < 0.01$, $Z = 13.87$, $p < 0.01$, WMD = −0.77, 95%CI: −0.88 − −0.66, and the difference is statistically significant (Fig. 14). The results indicated that whether the average age is more than 60 years old or not, the treatment with liraglutide in patients with type 2 diabetes is related to the smaller MODD.

SD: HbA1c: according to the level of HbA1c, patients were divided into two subgroups: HbA1c ≥ 9% and HbA1c < 9%. There were five studies involving 118 type 2 diabetic patients with HbA1C < 9%. The results were $F = 71\%$, $p < 0.01$, $Z = 4.18$, $p < 0.01$, WMD = −1.03, 95%CI: −1.51 − −0.55, and the difference was statistically significant. Two studies involved 75 patients with type 2 diabetes with HbA1c ≥ 9%. The results were $F = 99\%$, $p < 0.01$, $Z = 1.92$, $p = 0.05$, WMD = −1.25, 95%CI: −2.52 − −0.02, and the difference was not statistically significant (Fig. 15). It was suggested that the patients with type 2 diabetes mellitus whose HbA1c was less than 9% were related to the smaller SD. In type 2 diabetic patients with HbA1c ≥ 9%, the treatment with liraglutide was associated with smaller SD. b. Age:
Patients were divided into two subgroups according to whether the age was greater than 50 years. Three studies involved 103 patients with type 2 diabetes with an average age of less than 50 years. The results of heterogeneity test were $I^2 = 99\%$, $p < 0.01$, $Z = 2.60$, $p < 0.01$, $WMD = -1.41$, $95\% CI: -2.47 \text{ to } -0.35$, and the difference was statistically significant. Four studies involved 90 patients with type 2 diabetes with an average age of 50 years or older. The results of heterogeneity test were $I^2 = 68\%$, $p = 0.02$, $Z = 3.74$, $p < 0.01$, $WMD = -0.89$, $95\% CI: -1.36 \text{ to } -0.42$, and the difference was statistically significant (Fig. 16). The results indicated that the treatment with liraglutide in patients with type 2 diabetes was associated with smaller SD regardless of whether the average age was greater than 50 years.

In the existing studies, we collected and counted two indicators. One is the average daily compliance rate, the other is the proportion of hyperglycemia time (HAVC), and the results are as follows:

**Effect on HAVC and the proportion of hyperglycemia time in patients with type 2 diabetes**

Three studies involved 58 patients compared HAVC and the proportion of hyperglycemia time in patients with type 2 diabetes before and after treatment with liraglutide. Meta-analysis showed that the effect of liraglutide on HAVC and the proportion of hyperglycemia time in patients with type 2 diabetes was not significantly different from that before treatment with liraglutide ($F = 57\%$, $p = 0.10$, $Z = 7.55$, $p < 0.01$, $MD = -48.58$, $95\% CI: -61.2 \text{ to } -35.97$; Fig. 17; $F = 62\%$, $p = 0.11$, $Z = 395.79$, $p < 0.01$, $MD = 44.13$, $95\% CI: 41.71 \text{ to } 46.55$; Fig. 18). The above results may be related to the small number of research subjects, and indicates the need for large-scale experiments.

**Discussion**

This study conducted a meta-analysis of existing literature and concluded that the glycemic variability of type 2 diabetes patients who were treated with liraglutide was significantly different from that of type 2 diabetes patients who were not treated with liraglutide, indicating that the application of liraglutide was related to the smaller glycemic variability.

Currently, liraglutide is the most widely used GLP-1 RA [26] in the world, and it was approved by the European Medicines Agency for type 2 diabetes as early as 2009 [27]. Glycemic management strategies in patients with diabetes should aim to address the three major components of glycemic abnormalities: chronic hyperglycemia, hypoglycemia, and glycemic variability. These characteristics are closely related to the development and progression of diabetic complications [28]. Liraglutide monotherapy has been shown to reduce HbA1C and body weight as well as reduce the risk of hypoglycemic events. Adverse events commonly associated with liraglutide in clinical trials include nausea and hypoglycemia. Emerging data suggest that liraglutide may be a useful option for patients with T2DM [29]. The beneficial pharmacodynamic effects of liraglutide, including improved glucose-dependent glycemic control, reduced appetite and energy intake, and reduced postprandial lipids, made it a suitable treatment option for many patients with type 2 diabetes [7].

Type 2 diabetes is characterized by insulin resistance...
and progressive islet cell dysfunction leading to insulin deficiency [30]. Buteau et al. showed that GLP-1 can improve glucose stimulated insulin secretion, restore glucose capacity of glucose resistant β cells, and stimulate insulin gene expression and biosynthesis. In addition, GLP-1 plays the role of growth factor by promoting the proliferation, survival, and regeneration of β cells [31].

Chen et al. showed that liraglutide can improve glucose metabolism and insulin resistance in diabetic KKAy mice by stimulating insulin secretion, increasing glycogen production and glycolysis, and up-regulating GLUT4 expression [32]. Numerous studies have shown that endoplasmic reticulum stress is an important pathway for the induction and development of insulin resistance, and previous studies have confirmed the inevitable role of GLP-1 analogues in combating insulin resistance and endoplasmic reticulum stress [33]. In addition, studies have shown that weight loss can improve insulin resistance, reduce insulin secretion requirements, and may improve the effects of glucose and lipotoxicity on pancreatic beta cells [34]. Potts et al. further confirmed that GLP-1 receptor agonists may have weight-loss benefits in patients with type 2 diabetes [35]. It was found that GLP-1 receptor agonists affect weight loss through their effects on appetite and satiety [36]. GLP-1 is a kind of intestinal hypoglycemic hormone secreted from intestinal mucosa due to eating. It stimulates insulin secretion and inhibits glucagon secretion, both of which are glucose dependent. Studies by Degn et al. showed that liraglutide significantly reduced 24-hour circulating glucagon levels [37]. In a cross-sectional study, it has been reported that not only daily glucose variability such as MAGE but also day-to-day glucose variability such as MODD causes oxidative stress [38]. Furthermore, it has been reported that improvement of glucose variability leads to reduction of oxidative stress [39].

The results of Forbes et al. showed that fasting blood glucose variability was independently associated with all-cause mortality in Chinese patients with type 2 diabetes [40]. In the current knowledge and literature reports, improving blood glycemic variability is an important issue in the treatment of diabetes. Glycemic variability is a physiological phenomenon of great importance in diabetic patients, because it not only works to increase the average level of blood glucose, but also leads to the development of chronic diabetic complications. Although not confirmed, more “vulnerable” patients, such as the elderly and those with a higher potential cardiovascular risk, are likely to be the easiest to be exposed to the risk associated with hyperglycemic variability [41]. The effect of glycemic variability on the survival rate of elderly patients with type 2 diabetes is greater than that of metabolic control and the severity of hyperglycemia [9].

Currently, CGM is recommended for use in clinical practice: 1. patients with T1DM do not meet the target of HbA1c; 2. repeated episodes of hypoglycemia, or patients who require better glycemic control while avoiding hypoglycemia; 3. to get the best blood glucose control, for example, blood glucose control before or during pregnancy in women with T1DM or T2DM; 4. to improve the condition of brittle diabetes. CGM helps to reduce HbA1c, improve blood glucose control without increasing the risk of hypoglycemia, reduce glycemic
### Effect of liraglutide on GV in T2DM

#### Fig. 10 Subgroup analysis of MAGE: grouped by HbA1c

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% Cl | Mean Difference IV, Random, 95% Cl |
|-------------------|------|----|-------|------|----|-------|--------|---------------------------------|---------------------------------|
| **2.1.1 MAGE hba1c < 9** |      |    |        |      |    |        |        |                                 |                                 |
| Levti, S. pre2018 | 3.6  | 1.3| 18    | 4.81| 1.81| 18    | 5.9%   | -1.01 (-2.04, 0.02)              |                                 |
| Ma, Z pre2015    | 3.6  | 1.3| 31    | 5.22| 1.56| 31    | 7.0%   | -1.62 (-3.33, -0.91)            |                                 |
| Taniguchi, Y pre2011 | 2.68| 1.08| 80    | 4.55| 2.06| 80    | 7.4%   | -1.87 (-2.45, -1.29)            |                                 |
| Yingbo Yang pre2017 | 1.53| 0.46| 40    | 3.99| 0.59| 40    | 8.1%   | -2.36 (-2.56, -2.13)            |                                 |
| Jie Zhang pre2014 | 1.52| 0.27| 40    | 3.98| 0.52| 40    | 8.2%   | -2.46 (-2.64, -2.28)            |                                 |
| Guanghui Li pre2017 | 1.42| 0.45| 37    | 3.99| 1.48| 37    | 7.6%   | -2.57 (-3.07, -2.07)            |                                 |
| Xiaojiao Fan pre2019 | 2.53| 1.43| 42    | 5.42| 1.82| 42    | 7.0%   | -2.89 (-3.50, -2.28)            |                                 |
| Zhaosui Huang pre2016 | 3.2 | 1.7 | 28    | 7.6  | 4.1  | 28    | 4.1%   | -4.40 (-6.04, -2.76)            |                                 |
| Subtotal (95% CI) | 316  |    | 316   | 55.3 | -2.30 (-2.61, -2.00) |                                 |

Heterogeneity: Tau² = 0.11; Chi² = 23.26, df = 7 (P = 0.002); I² = 70%
Test for overall effect: Z = 14.69 (P < 0.00001)

#### Fig. 11 Subgroup analysis of MAGE: grouped by Age

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% Cl | Mean Difference IV, Random, 95% Cl |
|-------------------|------|----|-------|------|----|-------|--------|---------------------------------|---------------------------------|
| **2.2.1 MAGE age 40-50** |      |    |        |      |    |        |        |                                 |                                 |
| Jiaxing Xu pre2016 | 4.9  | 1.1| 30    | 6.5 | 1.1 | 30    | 7.4%   | -1.60 (-2.16, -1.04)            |                                 |
| Donghua Xu pre2019 | 3.6  | 1.4| 20    | 7.4  | 2.4 | 20    | 5.3%   | -3.80 (-5.02, -2.58)            |                                 |
| Shufang Xu pre2019 | 3.47 | 0.38| 45    | 7.58| 1.47| 45    | 7.7%   | -4.11 (-5.45, -2.76)            |                                 |
| Zhaosui Huang pre2016 | 3.2 | 1.7 | 28    | 7.6 | 4.1 | 28    | 4.1%   | -4.40 (-6.04, -2.76)            |                                 |
| Subtotal (95% CI) | 123  |    | 123   | 24.6 | -3.42 (-4.99, -1.84) |                                 |

Heterogeneity: Tau² = 2.30; Chi² = 50.84, df = 3 (P < 0.00001); I² = 94%
Test for overall effect: Z = 4.26 (P < 0.00001)

#### Fig. 11 Subgroup analysis of MAGE: grouped by Age

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% Cl | Mean Difference IV, Random, 95% Cl |
|-------------------|------|----|-------|------|----|-------|--------|---------------------------------|---------------------------------|
| **2.2.2 MAGE age 50-60** |      |    |        |      |    |        |        |                                 |                                 |
| Levti, S. pre2018 | 3.6  | 1.3| 18    | 4.81| 1.81| 18    | 5.9%   | -1.01 (-2.04, 0.02)              |                                 |
| Yan, L pre2015   | 3.18| 1.03| 25    | 4.2  | 2.19| 25    | 8.2%   | -1.02 (-1.97, -0.07)            |                                 |
| Jie Zhang pre2014 | 1.52| 0.27| 40    | 3.98| 0.52| 40    | 8.2%   | -2.46 (-2.64, -2.28)            |                                 |
| Guanghui Li pre2017 | 1.42| 0.45| 37    | 3.99| 1.48| 37    | 7.6%   | -2.57 (-3.07, -2.07)            |                                 |
| Xiaojiao Fan pre2019 | 2.53| 1.43| 42    | 5.42| 1.82| 42    | 7.0%   | -2.89 (-3.50, -2.28)            |                                 |
| Zhaosui Huang pre2016 | 3.7 | 1.5 | 20    | 11.3| 2.7 | 20    | 4.9%   | -5.28 (-6.51, -4.05)            |                                 |
| Subtotal (95% CI) | 202  |    | 202   | 45.1 | -3.13 (-4.08, -2.19) |                                 |

Heterogeneity: Tau² = 1.42; Chi² = 92.84, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 6.49 (P < 0.00001)

#### Fig. 11 Subgroup analysis of MAGE: grouped by Age

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% Cl | Mean Difference IV, Random, 95% Cl |
|-------------------|------|----|-------|------|----|-------|--------|---------------------------------|---------------------------------|
| **2.2.3 MAGE age >60** |      |    |        |      |    |        |        |                                 |                                 |
| Ma, Z pre2015    | 3.6  | 1.3| 31    | 5.22| 1.56| 31    | 7.0%   | -1.62 (-3.33, -0.91)            |                                 |
| Taniguchi, Y pre2011 | 2.08| 1.68| 80    | 4.55| 2.06| 80    | 7.4%   | -1.87 (-2.45, -1.29)            |                                 |
| Taniguchi, Y pre2011 | 1.81| 0.36| 10    | 3.96| 0.52| 10    | 7.6%   | -2.15 (-2.54, -1.76)            |                                 |
| Yingbo Yang pre2017 | 1.53| 0.45| 40    | 3.99| 0.58| 40    | 8.1%   | -2.36 (-2.59, -2.13)            |                                 |
| Subtotal (95% CI) | 161  |    | 161   | 30.3 | -2.12 (-2.41, -1.82) |                                 |

Heterogeneity: Tau² = 0.04; Chi² = 5.65, df = 3 (P = 0.13); I² = 47%
Test for overall effect: Z = 14.06 (P < 0.00001)

#### Fig. 11 Subgroup analysis of MAGE: grouped by Age
variability, and generally improve the quality of life of diabetic patients [6]. Evidence from previous studies shows that simple control of HbA1c does not reduce the risk of diabetic macrovascular complications [42]. Compared with stable hyperglycemia, the fluctuation of blood glucose significantly increased the level of oxidative stress in diabetic patients [43]. Studies have found that large blood glucose fluctuations trigger the production of nitrotyrosine and induce the expression of adhesion molecules and IL-6 compared with stable hyperglycemia [44]. Other studies have shown that reducing glycemic variability can improve the prognosis of microvascular and macrovascular diabetic complications. Frequent fluctuations of blood glucose, accompanied by hypoglycemia, will affect the individual’s mood changes, leading to more diabetes complications, depression, and poor quality of life. In addition, studies have found that larger glycemic variability is associated with lower quality of life than the influence of HbA1c and 24-hour mean blood glucose [45].

Meta-analysis is a secondary literature analysis based on previous research evidence, and so there are limitations and biases in the analysis. The limitation of the analysis is that the number of patients involved is small, and the long-term effects of the treatment are unknown. Other characteristics that may affect blood glucose control are not considered, such as treatment status, smoking status, etc.

In conclusion, this meta-analysis showed that liraglutide has a positive correlation with small glycemic variability and has a certain degree of credibility. Although there are some biases that affect the accuracy of the results, it can still be suggested that glycemic variability seems to be the focus of future treatment, aimed at ach-

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Fig. 12 Subgroup analysis of LAGE: grouped by HbA1c

Fig. 13 Subgroup analysis of MODD: grouped by HbA1c
ieve greater efficacy in controlling the metabolic changes of diabetes and preventing related complications. And it can provide new references and guidance for future clinical work. Further research is necessary to verify the current results.

**Conclusion**

This study conducted a meta-analysis of existing literature and concluded that the use of liraglutide in patients with type 2 diabetes is associated with less glycemic variability. This article has shown the credibility of existing liraglutide studies and can guide clinical work to a certain extent. In clinical practice, individualized prevention and treatment need to be closely combined with the actual situation of the patient.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest. This study was supported by a grant from the Government-funded specialist leader training program, Hebei Medical Science Research Project (20190284).
References

1. Du Q, Wang YJ, Yang S, Zhao YY, Han P (2014) Liraglutide for the treatment of type 2 diabetes mellitus: a meta-analysis of randomized placebo-controlled trials. Adv Ther 31: 1182–1195.

2. Aronson R, Umpierrez G, Stager W, Kovatchev B (2019) Insulin glargine/lixisenatide fixed-ratio combination improves glycemic variability and control without increasing hypoglycaemia. Diabetes Obes Metab 21: 726–731.

3. Hu YM, Zhao LH, Zhang XL, Cai HL, Huang HY, Xu F, et al. (2018) Association of glycemic variability evaluated by continuous glucose monitoring with diabetic peripheral neuropathy in type 2 diabetic patients. Endocrine 60: 292–300.

4. Hirsch IB (2015) Glycemic variability and diabetes complications: does it matter? of course it does! Diabetes care 38: 1610–1614.

5. Li M, Yang Y, Jiang D, Ying M, Wang Y, et al. (2017) Efficacy and safety of liraglutide versus sitagliptin both in combination with metformin in patients with type 2 diabetes: a systematic review and meta-analysis. Medicine 96: e8161.

6. Inchiostro S, Candido R, Cavalot F (2013) How can we monitor glycaemic time before and after treatment with liraglutide?

7. Jacobsen LV, Flint A, Olsen AK, Ingwersen SH (2016)
Liraglutide in type 2 diabetes mellitus: clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 55: 657–672.

8. Guthrie R (2018) Practice pearl: liraglutide and cardiovascular and renal events in type 2 diabetes. *Postgrad Med* 130: 154–158.

9. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM (2014) Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. *Diabetes Obes Metab* 16: 900–909.

10. Yu DH (2016) Blood glucose detection and safety analysis of liraglutide combined with insulin in the treatment of type 2 diabetes. *Capital Food Medicine* 20: 58–59 (In Chinese).

11. Li GH, Yu Y, Li XH, Lai YW, Yu L (2017) Effects of liraglutide on islet β-cell function and blood glucose fluctuations in patients with poor glycemic control in type 2 diabetes. *Journal of North Pharmacy* 10: 12–13 (In Chinese).

12. Wu JM, Ma YN, Dong LL, Tang HX (2016) Efficacy of liraglutide in the treatment of early-onset type 2 diabetes mellitus and its effects on blood glucose and islet function. *Hainan Medical Journal* 17: 2838–2840 (In Chinese).

13. Ma Z, Chen R, Liu Y, Yu P, Chen L (2015) Effect of liraglutide vs. NPH in combination with metformin on blood glucose fluctuations assessed using continuous glucose monitoring in patients with newly diagnosed type 2 diabetes. *Int J Clin Pharmacol Ther* 53: 933–939.

14. Huang Q, Li JW, Zhang L, Huang FC, Liu W, et al. (2018) Analysis of blood glucose changes and safety during the treatment of type 2 diabetes with liraglutide combined with insulin. *Hebei Medical Journal* 07: 1016–1019 (In Chinese).

15. Yu SF (2019) Clinical efficacy and safety of liraglutide in the treatment of patients with type 2 diabetes with poor glycemic control. *Journal of Hunan Normal University (Medical Sciences)* 02: 57–60 (In Chinese).

16. Yan L, Wang S, Chen P, Chen C, Shao Z, et al. (2015) The efficacy and safety of human glucagon-like peptide-1 analogue liraglutide in newly diagnosed type 2 diabetes with glycosylated hemoglobin A1c > 9. *Chin J Intern Med* 54: 307–312 (In Chinese).

17. Yang YB, Tian XY, Huang YZ, Li J, Li H, et al. (2017) Clinical study of liraglutide combined with insulin and glipizide in the treatment of elderly patients with hypothyroidism and type 2 diabetes. *China Pharmacy* 14: 1958–1961 (In Chinese).

18. Huang ZS, Yang J, Huang ZW, Yan LL, Wang CY, et al. (2016) Clinical efficacy of liraglutide in patients with poor glycemic control of T2MD with obesity. *Chinese Journal of Clinical Pharmacology and Therapeutics* 01: 87–92 (In Chinese).

19. Zhang J, Zhao V, Zhou V, Dong V, Kang Y, et al. (2015) Effects of liraglutide on islet β-cell function and blood glucose fluctuation in type 2 diabetic patients with poor glycemic control. *Chinese Journal of Diabetes* 06: 527–529 (In Chinese).

20. Fan XX, Yao YL, Hu YJ, Liu XL, Wang SQ, et al. (2018) Dynamic blood glucose monitoring of liraglutide and exenatide in patients with overweight/obesity type 2 diabetes Observation of curative effect. *Chinese Journal of Diabetes* 08: 637–639 (In Chinese).

21. Yu TY, Qiao Feng, Li XM, Ren YL, Liu X (2019) Huangqi Xiaoke Decoction combined with liraglutide for glucose and lipid metabolism and serum adipokinetines in type 2 diabetic patients with HbA1c still not meeting the standard after oral administration of various hypoglycemic agents Impact. *Modern Journal of Integrated Traditional Chinese and Western Medicine* 05: 485–489+99 (In Chinese).

22. Taniguchi Y, Mori Y, Sezaki K (2011) The effect of the human GLP-1 analogue liraglutide on 24-hour glycemic variations in Japanese type 2 diabetic, obese patients as assessed by continuous glucose monitoring (CGM). *Diabetes* 60: A310.

23. Mori Y, Taniguchi Y, Sezaki K, Yokoyama J, Usunomiya K (2011) Liraglutide narrows the range of circadian glycemic variations in Japanese type 2 diabetes patients and nearly flattens these variations in drug-naive type 2 diabetes patients: a continuous glucose monitoring-based study. *Diabetes Technol Ther* 13: 1139–1144.

24. Levit S, Ginosar G, Zivony A, Barnea R, Korek-Abadi I, et al. (2018) Cgm may serve as a “gold standard” tool, confirming metabolic recovery and restoration of functional ability and secretion of endogenous insulin in T2DM patients. *Diabetes Technol Ther* 20: A34–A35.

25. Funakoshi S, Hashiguchi J, Ikeda K, Harada T, et al. (2015) Superior effects with combination of insulin degludec (IDeg) and liraglutide (Lira) (IDeg + Lira) compared with basal-bolus insulin therapy (BB) in hemodialysis (HD) patients with poorly controlled type 2 diabetes (T2D): an assessment by continuous glucose. *Diabetes* 64: A45.

26. Ostwal A, Mocевич Е, Kragh N, Xu W (2016) Clinical effectiveness of liraglutide in type 2 diabetes treatment in the real-world setting: a systematic literature review. *Diabetes Ther* 7: 411–438.

27. Barnett AH (2012) The role of GLP-1 mimetics and basal insulin analogues in type 2 diabetes mellitus: guidance from studies of liraglutide. *Diabetes Obes Metab* 14: 304–314.

28. Ceriello A, Monnier L, Owens D (2019) Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol* 7: 221–230.

29. Blonde L, Russell-Jones D (2009) The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies. *Diabetes Obes Metab* 11: 26–34.

30. Ferrannini E (1998) Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. *Endocr Rev* 19: 477–490.

31. Buteau J (2008) GLP-1 receptor signaling: effects on pancreatic beta-cell proliferation and survival. *Diabetes
32. Chen LN, Lyu J, Yang XF, Ji WJ, Yuan BX, et al. (2013) Liraglutide ameliorates glycometabolism and insulin resistance through the upregulation of GLUT4 in diabetic KKAY mice. *Int J Mol Med* 32: 892–900.

33. Yang J, Ao N, Du J, Wang X, He Y (2015) Protective effect of liraglutide against ER stress in the liver of high-fat diet-induced insulin-resistant rats. *Endocrine* 49: 106–118.

34. Kim SH, Liu A, Ariel D, Abbasi F, Lamendola C, et al. (2014) Pancreatic beta cell function following liraglutide-augmented weight loss in individuals with prediabetes: analysis of a randomised, placebo-controlled study. *Diabetologia* 57: 455–462.

35. Potts JE, Gray LJ, Brady EM, Khunti K, Davies MJ, et al. (2015) The effect of glucagon-like peptide 1 receptor agonists on weight loss in type 2 diabetes: a systematic review and mixed treatment comparison meta-analysis. *PloS One* 10: e0126769.

36. Janssen P, Rotondo A, Mule F, Tack J (2013) Review article: a comparison of glucagon-like peptides 1 and 2. *Aliment Pharmacol Ther* 37: 18–36.

37. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, et al. (2004) One week’s treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53: 1187–1194.

38. Ohara M, Fukue T, Ouchi M, Watanabe K, Suzuki T (2016) Relationship between daily and day-to-day glycemic variability and increased oxidative stress in type 2 diabetes. *Diabetes Res Clin Pract* 122: 62–70.

39. Ohara M, Nagaika H, Goto S, Fukase A, Tanabe, Y (2018) Improvements of ambient hyperglycemia and glycemic variability are associated with reduction in oxidative stress for patients with type 2 diabetes. *Diabetes Res Clin Pract* 139: 253–261.

40. Forbes A, Murrells T, Mulnier H, Sinclair AJ (2018) Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. *Lancet Diabetes Endocrinol* 6: 476–486.

41. Frontoni S, Di Bartolo P, Avogaro A, Bosi E, Paolisso G, et al. (2013) Glucose variability: an emerging target for the treatment of diabetes mellitus. *Diabetes Res Clin Pract* 102: 86–95.

42. Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, et al. (2019) Intensive glucose control in patients with type 2 diabetes—15-year follow-up. *N Engl J Med* 380: 2215–2224.

43. Monnier L, Mas E, Ginet C, Michel F, Villon L, et al. (2006) Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295: 1681–1687.

44. Piconi L, Quagliaro L, Da Ros R, Assaloni R, Giugliano D, et al. (2004) Intermittent high glucose enhances ICAM-1, VCAM-1, E-selectin and interleukin-6 expression in human umbilical endothelial cells in culture: the role of poly (ADP-ribose) polymerase. *J Thromb Haemost* 2: 1453–1459.

45. Satya Krishna SV, Kota SK, Modi KD (2013) Glycemic variability: clinical implications. *Indian J Endocrinol Metab* 17: 611–619.