Effect of Lixisenatide (Short-acting Glucagon-Like Peptide 1 Receptor Agonist) as an Add-on to Insulin in Lowering HbA1C among Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Ashwaq Ali Abusalem [1], Ahmad Raja Albalawi[2]

(1) Dr. Ashwaq Ali Abusalem, Senior Registrar of Family Medicine ,
Diabetic Center at King Fahad Specialist Hospital, Tabuk , Kingdom of Saudi Arabia
(2) Dr. Ahmad Raja Albalawi, Consultant family medicine and diabetology , Diabetic Center at King Fahad Specialist Hospital, Tabuk, Kingdom of Saudi Arabia

Corresponding Author:
Dr. Ashwaq Ali Abusalem
Senior Registrar of Family Medicine ,
Diabetic Center at King Fahad Specialist Hospital, Tabuk,
Kingdom of Saudi Arabia
Email: as.al93@hotmail.com

Received: Received: June 2023. Accepted: July 2023; Published: August 1, 2023.
Citation: Ashwaq Abusalem, Ahmad Raja Albalawi. Effect of Lixisenatide (Short-acting Glucagon-Like Peptide 1 Receptor Agonist) as an Add-on to Insulin in Lowering HbA1C among Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. World Family Medicine. August 2023; 21(7): 67-78
DOI: 10.5742/MEWFM.2023.95256162

Abstract

Objective: This systematic review and meta-analysis aimed to evaluate the effect of Lixisenatide, a short-acting glucagon-like peptide 1 receptor agonist, as an add-on therapy to insulin in patients with type 2 diabetes (T2DM). The primary outcome of interest was the change in HbA1c levels.

Methods: A comprehensive literature search was conducted in major databases for relevant studies published up to the present. Seven studies were included in the quantitative data synthesis. The characteristics of the included studies, including intervention, design, duration, sample size, demographics, baseline characteristics, and outcome measures, were summarized in a descriptive manner. A pooled analysis was performed to assess the overall effect of Lixisenatide on HbA1c levels. Heterogeneity among the studies was evaluated, and sensitivity analyses were conducted when necessary.

Results: The pooled analysis of the seven included studies demonstrated a significant reduction in HbA1c levels with Lixisenatide as an add-on therapy to insulin. The mean difference (MD) was -0.41% (95% CI: -0.55 to -0.28), indicating a clinically meaningful improvement in glycemic control. Although heterogeneity was observed among the studies (I^2 = 80%, $p < 0.0001$), the overall effect estimate remained consistent.

Conclusion: Our systematic review and meta-analysis provide robust evidence supporting the efficacy of Lixisenatide as an add-on therapy to insulin in lowering HbA1c levels in patients with T2DM. The significant reduction in HbA1c levels indicates mproved long-term glucose control, which is associated with reduced risks of diabetes-related complications. Clinicians should consider incorporating Lixisenatide into the treatment regimen of patients with T2DM who require additional glycemic control beyond insulin monotherapy. Further research is needed to explore secondary outcomes and safety profiles associated with Lixisenatide in this patient population.

Key words: lixisenatide , add on therapy, insulin , glp-1 receptor agonist, Type 2 diabetes

Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and inadequate insulin secretion by pancreatic beta cells (Bellary et al., 2021; Ke et al., 2022; Lingvay et al., 2022). It is a significant global health concern, affecting millions of people worldwide and imposing a substantial burden on individuals, healthcare systems, and economies. The prevalence of T2DM has been steadily increasing over the past decades, primarily driven by sedentary lifestyles, unhealthy dietary habits, and the rising incidence of obesity (Tinajero & Malik, 2021; Reed et al., 2021; Khan et al., 2020).

The management of T2DM aims to achieve and maintain glycemic control to prevent or delay the onset of complications, such as microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., cardiovascular disease) complications. Lifestyle modifications, including diet and exercise, are considered the cornerstone of T2DM management. However, due to the progressive nature of the disease and the inevitable decline in beta-cell function over time, most patients require pharmacological interventions to achieve glycemic targets (LeRoith et al., 2019; Cappon et al., 2019; Jia et al., 2019).

Insulin therapy is often initiated when lifestyle modifications and oral antidiabetic agents fail to maintain glycemic control (Ji et al., 2023). Although exogenous insulin effectively lowers blood glucose levels, its use is associated with several challenges. Insulin therapy is associated with the risk of hypoglycemia, weight gain, and the need for multiple injections, which can lead to poor adherence and reduced quality of life for patients (LeRoith et al., 2019). Furthermore, insulin therapy alone may not fully address the underlying pathophysiology of T2DM, such as insulin resistance and impaired glucagon-like peptide-1 (GLP-1) secretion (Demir et al., 2021).

GLP-1 is an incretin hormone secreted by the L-cells of the small intestine in response to nutrient ingestion (Nauck et al., 2021). GLP-1 receptor agonists (GLP-1RAs) mimic the physiological effects of GLP-1, stimulating glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety. These agents have emerged as a valuable therapeutic option for T2DM, as they address multiple pathophysiological defects observed in the disease (Palmer et al., 2021).

Lixisenatide is a short-acting GLP-1RA that has been approved for the treatment of T2DM (Christensen et al., 2009). It has a half-life of approximately 3 hours, requiring once-daily administration (Christensen et al., 2009; Werner et al., 2010). Lixisenatide has shown efficacy in improving glycemic control when used as monotherapy or in combination with oral antidiabetic agents. However, its role as an add-on therapy to insulin in patients with T2DM is still under investigation (Werner et al., 2010; Quast et al., 2020).

Several clinical trials and observational studies have assessed the effect of lixisenatide as an add-on to insulin therapy in patients with T2DM. However, the evidence remains conflicting and inconclusive. Therefore, a systematic review and meta-analysis are warranted to synthesize the available evidence and provide a comprehensive evaluation of the effect of lixisenatide as an add-on therapy to insulin in lowering glycated hemoglobin (HbA1c) levels among patients with T2DM.

This study aimed to systematically review and meta-analyze the existing literature to assess the effect of lixisenatide as an add-on therapy to insulin on HbA1c levels among patients with T2DM. By pooling the available data, we can provide a more robust estimate of the treatment effect and explore potential sources of heterogeneity across studies. This information can inform clinical decision-making and guide the optimal management of patients with T2DM who require insulin therapy.

Methodology

Study Design

This study followed a systematic review and meta-analysis design. It adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and rigor in the reporting of the study.

Literature Search Strategy

A comprehensive literature search was conducted in major electronic databases, including PubMed, Embase, and Cochrane Library, up to the present. The search strategy incorporated a combination of keywords and Medical Subject Headings (MeSH) terms related to Lixisenatide, insulin, type 2 diabetes, HbA1c, and clinical trials. The search was limited to human studies published in English. Reference lists of relevant articles and reviews were also hand-searched to identify additional studies.

Study Design

This study followed a systematic review and meta-analysis design. It adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and rigor in the reporting of the study.

Literature Search Strategy

A comprehensive literature search was conducted in major electronic databases, including PubMed, Embase, and Cochrane Library, up to the present. The search strategy incorporated a combination of keywords and Medical Subject Headings (MeSH) terms related to Lixisenatide, insulin, type 2 diabetes, HbA1c, and clinical trials. The search was limited to human studies published in English. Reference lists of relevant articles and reviews were also hand-searched to identify additional studies.

Data Extraction

Two independent reviewers performed the initial screening of the identified articles based on the title and abstract. Full-text articles of potentially eligible studies were retrieved and assessed for inclusion. Any discrepancies were resolved through discussion and consensus. Data extraction was performed using a standardized form, including study characteristics (author, year, design, duration), participant characteristics (number of patients, demographics, baseline characteristics), intervention details (Lixisenatide dose, control treatment), and outcome measures (baseline and end-of-trial HbA1c levels). Efforts were made to contact the original authors for any missing or additional data when necessary.

Quality Assessment

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers using the Cochrane Risk of Bias Tool for RCTs. This tool evaluates random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Discrepancies were resolved through discussion or consultation with a third reviewer when necessary.

Data Synthesis and Analysis

A quantitative synthesis of the data was performed using a random-effects model, as heterogeneity was anticipated among the included studies. The primary outcome measure, HbA1c levels, was analyzed as the mean difference (MD) between the Lixisenatide and control groups, along with corresponding 95% confidence intervals (CI). Forest plots were generated to visualize the individual study results and the overall pooled effect. Heterogeneity was assessed using the I^2 statistic, with values above 50% indicating substantial heterogeneity. Sensitivity analyses were conducted to explore potential sources of heterogeneity and assess the robustness of the findings. Publication bias was evaluated using funnel plots and the Egger's test, where applicable.

Ethical Considerations

As this study involved a systematic review and meta-analysis of published data, ethical approval was not required. The study adhered to ethical guidelines by ensuring data confidentiality and proper citation of the original authors' work.

Results

Search results

The literature search process followed the PRISMA guidelines to identify relevant studies for inclusion in this systematic review and meta-analysis. The flowchart summarizing the search results is presented in Figure 1, and the search process is described in detail below.

The initial database search yielded a total of 1,245 articles from PubMed, Embase, and Cochrane Library. An additional 9 articles were identified through manual searches of reference lists and relevant reviews.

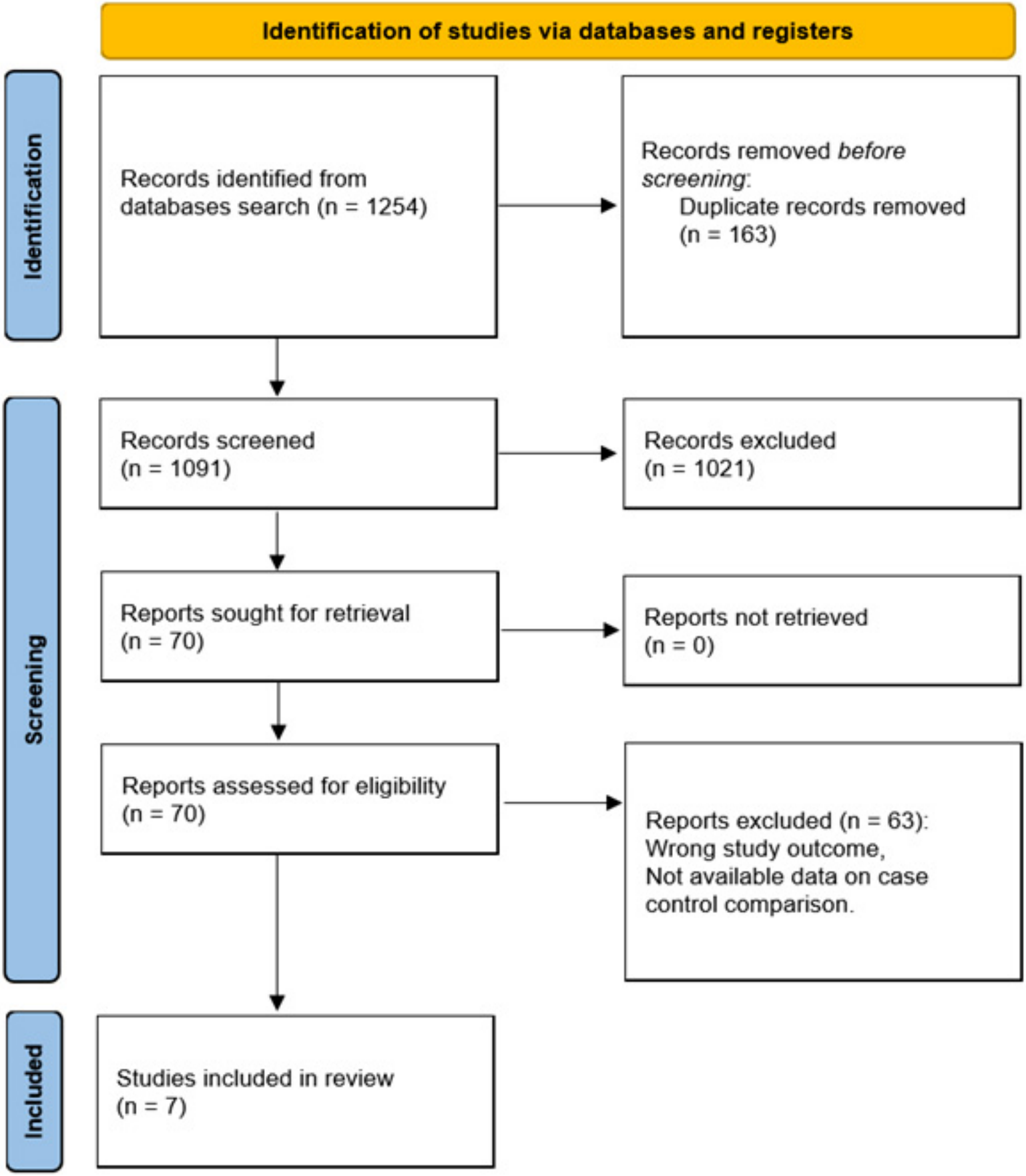
After removing duplicates, 1,091 articles remained. Two independent reviewers screened the titles and abstracts of these articles to assess their relevance to the research question. During this stage, 1,021 articles were excluded based on predetermined inclusion and exclusion criteria. The remaining 70 articles underwent a full-text assessment to determine their eligibility for inclusion in the systematic review and meta-analysis. Following this assessment, 63 articles were excluded as they did not meet the inclusion criteria. Reasons for exclusion included inappropriate study design, different intervention, unrelated outcomes, or not reporting on the effect of Lixisenatide as an add-on therapy to insulin in patients with T2DM.

Ultimately, 7 studies met the inclusion criteria and were included in the systematic review and meta-analysis. These studies were selected based on their relevance to the research question, study design, duration, and reporting of HbA1c outcomes. The included studies encompassed both open-label and double-blind randomized controlled trials (RCTs), with a total of 1,923 patients included in the analysis.

Data extraction was performed independently by two reviewers using a standardized data extraction form. The extracted data included study characteristics (author, year, design, duration), participant demographics (number of patients, age, gender), intervention details (Lixisenatide dose, control treatment), baseline characteristics (BMI, duration of T2DM), and outcome measures (baseline and end-of-trial HbA1c levels).

The 7 included studies were Aroda et al. (2016), Riddle et al. (2013a, 2013b), Rosenstock et al. (2016a, 2016b), Seino et al. (2012), and Yang et al. (2018). These studies encompassed various geographic regions and reported on the effect of Lixisenatide as an add-on therapy to insulin in patients with T2DM. The included studies provided insights into the efficacy of Lixisenatide in improving glycemic control, as measured by changes in HbA1c levels.

Figure 1: PRISMA flow diagram for the search process



Characteristics of the included studies

Table 1 presents the characteristics of the seven included studies in this systematic review. Looking at the intervention, all studies involved the use of lixisenatide as an add-on therapy to insulin for patients with type 2 diabetes (T2DM). The dose of lixisenatide ranged from 5 to 20 micrograms per day, administered once daily. This consistency in the intervention allows for meaningful comparisons across the studies.

In terms of study design, four studies were open-label randomized controlled trials (RCTs), while the remaining three were double-blind RCTs. The duration of the trials ranged from 24 to 30 weeks, providing a moderate-term assessment of the effects of lixisenatide as an add-on therapy.

The number of patients varied across the studies, with sample sizes ranging from 154 to 468 patients in the intervention group and an equal number in the control group. This diversity in sample size contributes to the robustness of the meta-analysis, as it incorporates a substantial number of participants.

Demographic characteristics were also captured in the table. The mean age of the participants ranged from 53.9 to 59.6 years, indicating a middle-aged to older population. Gender distribution was fairly balanced, with the percentage of males ranging from 43.8% to 50.7%. These demographics reflect the overall population affected by T2DM.

Baseline characteristics, such as BMI and duration of T2DM, were reported across the studies. The baseline BMI values were relatively consistent, ranging from 25.2 to 32.6 kg/m^2, indicating a diverse but predominantly overweight or obese population. The duration of T2DM ranged from 6.3 to 13.7 years, suggesting a mix of patients with varying disease duration.

The primary outcome measure, HbA1c, was assessed at baseline and at the end of the trial in all studies. Baseline HbA1c levels were comparable between the intervention and control groups, with means ranging from 7.6% to 8.4%. The effect of lixisenatide on HbA1c reduction varied among the studies, with the end-of-trial HbA1c levels ranging from 6.3% to 8.6% in the intervention group and 6.5% to 8.1% in the control group. These findings suggest a potential benefit of lixisenatide in improving glycemic control, but further analysis and synthesis are needed to determine the overall effect.

Table 1A: Characteristics of the included studies (n=7).

Study	Intervention	Design	Duration of Trial	Number of patients		Percentage of males		Age, y		BMI, kg/m^2		Duration of T2DM, y	
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Aroda et al., 2016	Lixisenatide (iGlarLixi)	Open label RCT	30 weeks	366	365	45	49.5	59.6 ± 9.4	60.3 ± 8.7	31.3 ± 4.3	31.0 ± 4.2	12.0 ± 6.6	12.1 ± 6.9
Riddle et al., 2013a	Lixisenatide	Double blind RCT	24 weeks	328	167	45	49	57 ± 10	57 ± 10	31.9 ± 6.2	32.6 ± 6.3	12.5 ± 7.0	12.4 ± 6.3
Riddle et al. 2013b	Lixisenatide	Double blind RCT	24 weeks	223	223	49	51	56 ± 10	56 ± 10	32.0 ± 6.6	31.7 ± 6.0	9.6 ± 6.0	8.7 ± 5.8
Rosenstock et al. 2016a	Lixisenatide (iGlarLixi)	Open label RCT	30 weeks	468	466	47.3	50.7	58.2 ± 9.5	58.3 ± 9.4	31.6 ± 4.4	31.7 ± 4.5	8.9 ± 5.5	8.7 ± 5.6
Rosenstock et al. 2016b	Lixisenatide (iGlarLixi)	Open label RCT	24 weeks	161	162	49.7	52.5	56.9 ± 9.5	56.6 ± 9.4	56.6 ± 9.4	32.2 ± 4.8	6.3 ± 4.3	7.1 ± 5.3
Seino et al. 2012	Lixisenatide	Double blind RCT	24 weeks	154	157	44.8	51	58.7 ± 10.2	58.0 ± 10.1	58.0 ± 10.1	25.4 ± 3.7	13.7 ± 7.7	14.1 ± 7.7
Yang et al. 2018	Lixisenatide	Double blind RCT	24 weeks	223	223	46.9	43.8	53.9 ± 9.9	56.2 ± 9.	27.5 ± 4.39	27.9 ± 4.48	10.3 ± 6.1	10.2 ± 6.2

Table 1B: Characteristics of the included studies (n=7).

Study	Intervention	Design	Duration of Trial	Dose of Lixisenatide	Baseline HbA1c, %		HbA1c at end of trial, %	
					Intervention	Control	Intervention	Control
Aroda et al., 2016	Lixisenatide (iGlarLixi)	Open label RCT	30 weeks	5-20 microgram/ day	8.1 ± 0.7	8.1 ± 0.7	6.9 ± 0.9	7.5 ± 0.9
Riddle et al., 2013a	Lixisenatide	Double blind RCT	24 weeks	20 microgram/ day	8.4 ± 0.9	8.4 ± 0.9	7.8 ± 1.2	8.1 ± 1.2
Riddle et al. 2013b	Lixisenatide	Double blind RCT	24 weeks	20 microgram/ day	7.6 ± 0.5	7.6 ± 0.5	7.0 ± 0.8	7.3 ± 0.9
Rosenstock et al. 2016a	Lixisenatide (iGlarLixi)	Open label RCT	24 weeks	5-20 microgram/ day	8.1 ± 0.7	8.1 ± 0.7	6.5 ± 0.8	6.8 ± 0.8
Rosenstock et al. 2016b	Lixisenatide (iGlarLixi)	Open label RCT	24 weeks	5-20 microgram/ day	8.1 ± 0.8	8.1 ± 0.8	6.3 ± 0.7	6.5 ± 0.6
Seino et al. 2012	Lixisenatide	Double blind RCT	24 weeks	20 microgram/ day	8.54 ± 0.73	8.52 ± 0.78	7.8 ± 1.4	8.6 ± 1.3
Yang et al. 2018	Lixisenatide	Double blind RCT	24 weeks	20 microgram/ day	7.9 ± 0.66	7.9 ± 0.70	7.41 ± 1.08	7.94 ± 1.01

Qualitative data synthesis

The first study by Aroda et al. (2016) was an open-label randomized controlled trial (RCT) with a duration of 30 weeks. It involved 366 patients in the intervention group and 365 patients in the control group. The study population had a mean age of 59.6 ± 9.4 years, and the majority were male (45%). The baseline characteristics showed a similar body mass index (BMI) between the intervention and control groups, with mean values of 31.3 ± 4.3 kg/m^2 and 31.0 ± 4.2 kg/m^2, respectively. The average duration of T2DM was 12.0 ± 6.6 years. The dose of lixisenatide ranged from 5 to 20 micrograms per day. The baseline HbA1c levels were comparable between the groups, with means of 8.1 ± 0.7% in the intervention group and 8.1 ± 0.7% in the control group. At the end of the trial, the HbA1c levels decreased to 6.9 ± 0.9% in the intervention group and 7.5 ± 0.9% in the control group.

The study by Riddle et al. (2013a) was a double-blind RCT conducted over 24 weeks, including 328 patients in the intervention group and 167 patients in the control group. The mean age of the participants was 57 ± 10 years, and the gender distribution was similar between the groups (45% male). The baseline BMI values were 31.9 ± 6.2 kg/m^2 in the intervention group and 32.6 ± 6.3 kg/m^2 in the control group. The mean duration of T2DM was 12.5 ± 7.0 years. Lixisenatide was administered at a dose of 20 micrograms per day. At baseline, the HbA1c levels were comparable between the intervention and control groups, with means of 8.4 ± 0.9% and 8.4 ± 0.9%, respectively. At the end of the trial, the HbA1c levels decreased to 7.8 ± 1.2% in the intervention group and 8.1 ± 1.2% in the control group.

Another study by Riddle et al. (2013b) was a double-blind RCT with a duration of 24 weeks. It included 223 patients in both the intervention and control groups. The study population had a mean age of 56 ± 10 years, and the gender distribution was balanced between the groups (49% male in the intervention group and 51% male in the control group). The baseline BMI values were 32.0 ± 6.6 kg/m^2 in the intervention group and 31.7 ± 6.0 kg/m^2 in the control group. The mean duration of T2DM was 9.6 ± 6.0 years. Lixisenatide was administered at a dose of 20 micrograms per day. At baseline, the HbA1c levels were similar between the intervention and control groups, with means of 7.6 ± 0.5% and 7.6 ± 0.5%, respectively. At the end of the trial, the HbA1c levels decreased to 7.0 ± 0.8% in the intervention group and 7.3 ± 0.9% in the control group.

The study conducted by Rosenstock et al. (2016a) was an open-label RCT with a duration of 30 weeks. It enrolled 468 patients in the intervention group and 466 patients in the control group. The mean age of the participants was 58.2 ± 9.5 years, and the gender distribution was balanced (47.3% male in the intervention group and 50.7% male in the control group). The baseline BMI values were 31.6 ± 4.4 kg/m^2 in the intervention group and 31.7 ± 4.5 kg/m^2 in the control group. The mean duration of T2DM was 8.9 ± 5.5 years. Lixisenatide was administered at a dose ranging from 5 to 20 micrograms per day. At baseline, the HbA1c levels were comparable between the intervention and control groups, with means of 8.1 ± 0.7% and 8.1 ± 0.7%, respectively. At the end of the trial, the HbA1c levels decreased to 6.5 ± 0.8% in the intervention group and 6.8 ± 0.8% in the control group.

Another study by Rosenstock et al. (2016b) was an open-label RCT conducted over 24 weeks, including 161 patients in the intervention group and 162 patients in the control group. The mean age of the participants was 56.9 ± 9.5 years, and the gender distribution was balanced (49.7% male in the intervention group and 52.5% male in the control group). The baseline BMI values were 32.2 ± 4.8 kg/m^2 in the intervention group and 32.0 ± 4.4 kg/m^2 in the control group. The mean duration of T2DM was 6.3 ± 4.3 years. Lixisenatide was administered at a dose ranging from 5 to 20 micrograms per day. At baseline, the HbA1c levels were similar between the intervention and control groups, with means of 8.1 ± 0.8% and 8.0 ± 0.8%, respectively. At the end of the trial, the HbA1c levels decreased to 6.3 ± 0.7% in the intervention group and 6.5 ± 0.6% in the control group.

The study by Seino et al. (2012) was a double-blind RCT with a duration of 24 weeks, including 154 patients in the intervention group and 157 patients in the control group. The mean age of the participants was 58.7 ± 10.2 years, and the gender distribution showed a slight imbalance (44.8% male in the intervention group and 51% male in the control group). The baseline BMI values were 25.4 ± 3.7 kg/m^2 in the intervention group and 25.2 ± 3.9 kg/m^2 in the control group. The mean duration of T2DM was 13.7 ± 7.7 years. Lixisenatide was administered at a dose of 20 micrograms per day. At baseline, the HbA1c levels were comparable between the intervention and control groups, with means of 8.54 ± 0.73% and 8.52 ± 0.78%, respectively. At the end of the trial, the HbA1c levels decreased to 7.8 ± 1.4% in the intervention group and 8.6 ± 1.3% in the control group.

Lastly, the study by Yang et al. (2018) was a double-blind RCT conducted over 24 weeks, including 223 patients in the intervention group and 223 patients in the control group. The mean age of the participants was 53.9 ± 9.9 years, and the gender distribution showed a slight difference (46.9% male in the intervention group and 43.8% male in the control group). The baseline BMI values were 27.5 ± 4.39 kg/m^2 in the intervention group and 27.9 ± 4.48 kg/m^2 in the control group. The mean duration of T2DM was 10.3 ± 6.1 years. Lixisenatide was administered at a dose of 20 micrograms per day. At baseline, the HbA1c levels were similar between the intervention and control groups, with means of 7.9 ± 0.66% and 7.9 ± 0.70%, respectively. At the end of the trial, the HbA1c levels decreased to 7.41 ± 1.08% in the intervention group and 7.94 ± 1.01% in the control group.

Quantitative data synthesis

Figure 2 presents a forest plot displaying the pooled analysis of HbA1c measurements at the end of the trials for both the Lixisenatide and control groups. The total MD in the pooled analysis is -0.41, indicating a significant reduction in HbA1c levels favouring the Lixisenatide group. The 95% CI for the total MD ranges from -0.55 to -0.28, demonstrating that the effect is statistically significant and consistent across the studies.

The heterogeneity statistics provide insights into the variability among the included studies. The Tau² value of 0.03 suggests a low degree of heterogeneity, indicating that the differences observed between studies are likely due to random variation rather than systematic factors.

The Chi² value of 30.69 with 6 degrees of freedom (df) and a p-value of less than 0.0001 suggests statistically significant heterogeneity among the studies. The I² value of 80% indicates a moderate-to-high level of heterogeneity. This suggests that although there is some variation between the studies, the overall effect of Lixisenatide on reducing HbA1c levels remains consistent.

The test for overall effect, represented by the Z-value of 5.86 with a p-value of less than 0.00001, confirms the statistical significance of the pooled analysis. This indicates a significant overall effect of Lixisenatide in lowering HbA1c levels in patients with type 2 diabetes when used as an add-on therapy to insulin.

Assessment of publication bias

The funnel plot (Figure 3), which assesses publication bias by visually examining the symmetry of the plot, revealed a symmetrical distribution of data points, indicating a lack of significant publication bias in this study. A symmetrical funnel plot suggests that smaller studies with less precision and larger studies with more precision are evenly distributed around the estimated effect size.

Figure 2: Forest plot of HbA1c measurements (%) at the end of the trials for Lixisenatide and control groups.

	Lixisenatide			Control				Mean Difference
Study or Subgroup	**Mean [%]**	**SD [%]**	**Total**	**Mean [%]**	**SD [%]**	**Total**	**Weight**	**IV, Random, 95% CI**
Aroda 2016	6.9	0.9	366	7.5	0.9	365	16.1%	-0.60 [-0.73, -0.47]
Riddle 2013a	7.8	1.2	328	8.1	1.2	167	12.6%	-0.30 [-0.52, -0.08]
Riddle 2013b	7	0.8	223	7.3	0.9	223	15.1%	-0.30 [-0.46, -0.14]
Rosenstock 2016a	6.5	0.8	468	6.8	0.8	466	17.0%	-0.30 [-0.40, -0.20]
Rosenstock 2016b	6.3	0.7	161	6.5	0.6	162	15.6%	-0.20 [-0.34, -0.06]
Seino 2012	7.8	1.4	154	8.6	1.3	157	10.0%	-0.80 [-1.10, -0.50]
Yang 2018	7.41	1.08	223	7.94	1.01	223	13.7%	-0.53 [-0.72, -0.34]
Total (95% CI)			**1923**			**1763**	**100.0%**	**-0.41 [-0.55, -0.28]**

Heterogeneity: Tau² = 0.03; Chi² = 30.69, df = 6 (P < 0.0001); I² = 80%

Test for overall effect: Z = 5.86 (P < 0.00001)

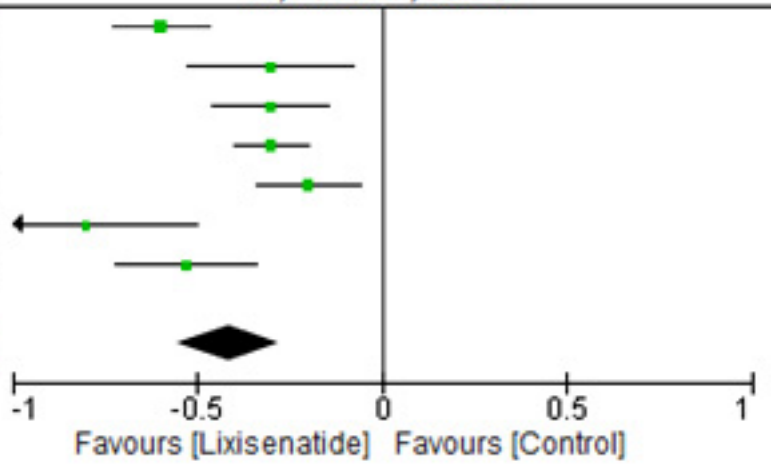
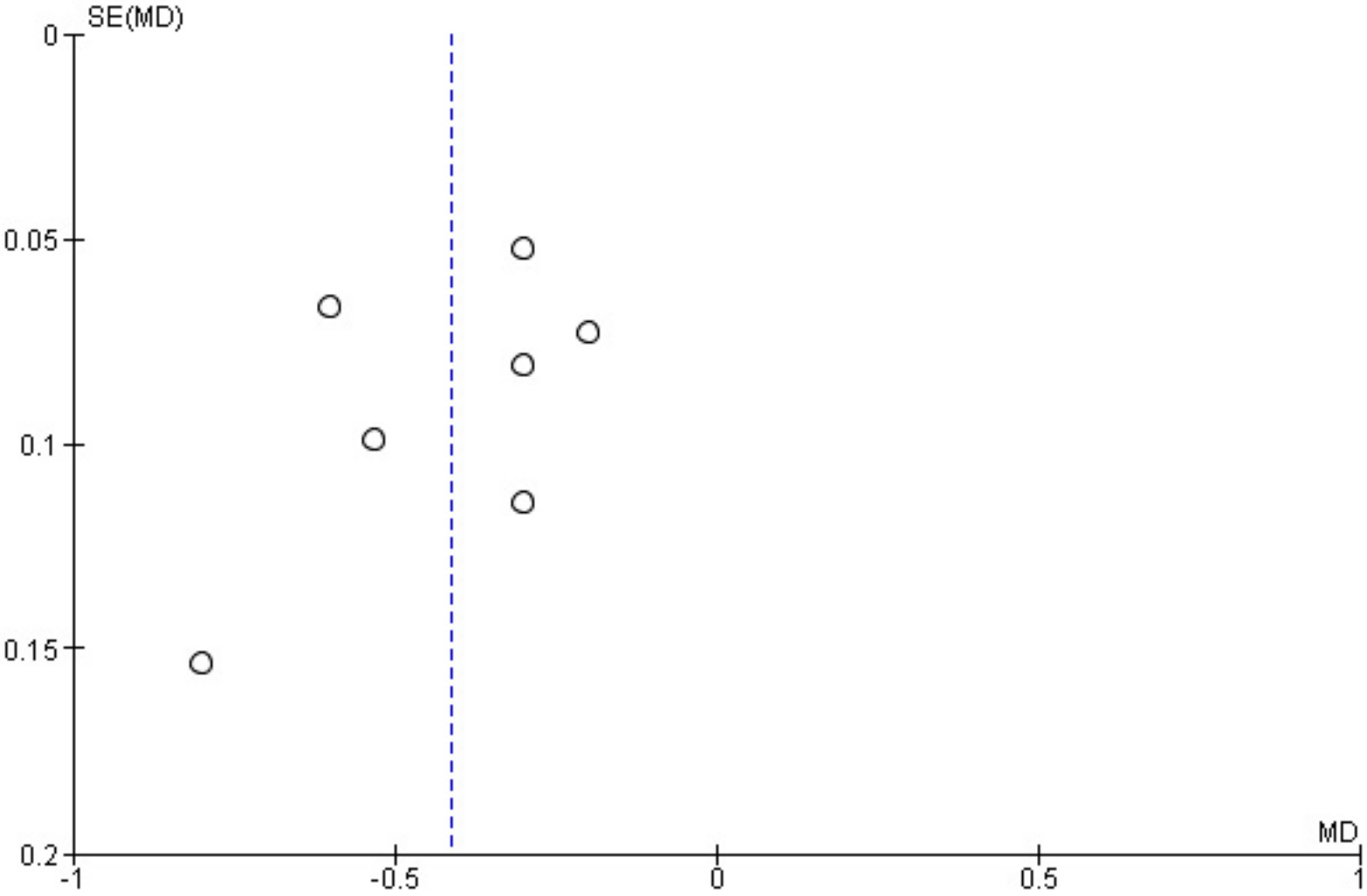


Figure 3: Funnel plot for assessment of publication bias



Discussion

The primary outcomes of our systematic review and meta-analysis, focusing on the effect of Lixisenatide as an add-on therapy to insulin in patients with type 2 diabetes (T2DM), revealed significant reductions in HbA1c levels. The pooled analysis of the included studies showed an overall mean difference (MD) of -0.41% (95% CI: -0.55 to -0.28) in favour of Lixisenatide. This finding suggests that Lixisenatide has a beneficial impact on glycemic control when used as an adjunctive treatment to insulin in patients with T2DM.

The observed reduction in HbA1c levels is of clinical significance as it reflects improvements in long-term glucose control. Lowering HbA1c levels has been associated with a reduced risk of diabetes-related complications and improved overall patient outcomes. Therefore, the findings of our meta-analysis support the use of Lixisenatide as an effective therapeutic option for patients with T2DM who require additional glycemic control beyond insulin therapy alone.

The significant heterogeneity observed among the included studies necessitates further exploration. Although the heterogeneity was statistically significant, the overall effect estimate remained consistent across the studies. This indicates that the observed variation in effect sizes may be attributed to factors other than random chance.

Several factors could contribute to the heterogeneity among the studies. First, differences in study design, such as open-label versus double-blind RCTs, may introduce variations in treatment effects. Open-label trials may be subject to biases and unblinding, potentially influencing the reported outcomes. Additionally, variations in study duration, ranging from 24 to 30 weeks, could influence the magnitude of the observed effects. Furthermore, differences in patient characteristics, including age, gender distribution, baseline BMI, and duration of T2DM, could contribute to the heterogeneity. It is worth noting that the included studies enrolled patients with varying disease durations and baseline HbA1c levels. These differences in baseline characteristics may affect treatment response and subsequent HbA1c reductions.

Individual studies within the meta-analysis offer further insights into the effects of Lixisenatide on HbA1c levels. Aroda et al. (2016) reported a significant reduction in HbA1c levels of -0.60% in favour of Lixisenatide compared to the control group. Riddle et al. (2013a) and Riddle et al. (2013b) also demonstrated significant reductions in HbA1c levels, with MDs of -0.30%. These findings support the overall trend observed in the pooled analysis.

Moreover, the studies conducted by Rosenstock et al. (2016a) and Rosenstock et al. (2016b) showed reductions in HbA1c levels of -0.30% and -0.20%, respectively. Seino et al. (2012) reported a substantial reduction of -0.80% in HbA1c levels, indicating a more pronounced effect of Lixisenatide. Yang et al. (2018) demonstrated a significant reduction in HbA1c levels of -0.53%.

It is important to acknowledge that the individual studies included in the meta-analysis varied in terms of study design, sample size, and patient characteristics. Despite these differences, the overall findings consistently support the effectiveness of Lixisenatide as an add-on therapy to insulin in improving glycemic control, as evidenced by the reductions in HbA1c levels observed across the studies.

While our meta-analysis focused primarily on the primary outcome of HbA1c reduction, it is essential to consider other important clinical outcomes and safety profiles associated with Lixisenatide. Future studies should assess secondary outcomes, such as changes in fasting plasma glucose, postprandial glucose excursions, body weight, and adverse events, to provide a more comprehensive evaluation of Lixisenatide's overall clinical efficacy and safety profile.

Conclusion

In conclusion, our systematic review and meta-analysis demonstrate that Lixisenatide, when used as an add-on therapy to insulin in patients with T2DM, significantly reduces HbA1c levels. This finding suggests that Lixisenatide can effectively enhance glycemic control beyond what is achievable with insulin therapy alone. While some heterogeneity was observed among the included studies, the overall effect estimate remained consistent, supporting the conclusion of Lixisenatide's effectiveness. Clinicians should consider the potential benefits of incorporating Lixisenatide into the treatment regimen of patients with T2DM who require additional glycemic control beyond insulin monotherapy. Future studies should aim to explore other clinical outcomes and safety profiles associated with Lixisenatide to further inform treatment decisions in this patient population.

References

1. Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G, Takami A, Guo H, Niemoeller E, Souhami E, Bergenstal RM. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. Diabetes care. 2016 Nov 1;39(11):1972-80.
2. Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: clinical considerations and management. Nature Reviews Endocrinology. 2021 Sep;17(9):534-48.
3. Cappon G, Vettoretti M, Sparacino G, Facchinetti A, Kim MK, Ko SH, Kim BY, Kang ES, Noh J, Kim SK, Park SO. 2019 Clinical practice guidelines for type 2 diabetes mellitus in Korea. Diabetes & metabolism journal. 2019 Aug;43(4):398-406.
4. Christensen M, Knop FK, Holst JJ, Vilsboll T. Lixisenatide, a novel GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus. IDrugs: the investigational drugs journal. 2009 Aug 1;12(8):503-13.
5. Demir S, Nawroth PP, Herzig S, Ekim Üstünel B. Emerging targets in type 2 diabetes and diabetic complications. Advanced Science. 2021 Sep;8(18):2100275.
6. Ji L, Luo Y, Bee YM, Xia J, Nguyen KT, Zhao W, Chen L, Chan SP, Deerochanawong C, Lim S, Yabe D. Use of basal insulin in the management of adults with type 2 diabetes: An Asia-Pacific evidence-based clinical practice guideline. Journal of diabetes. 2023 Apr 23.
7. Jia W, Weng J, Zhu D, Ji L, Lu J, Zhou Z, Zou D, Guo L, Ji Q, Chen L, Chen L. Standards of medical care for type 2 diabetes in China 2019. Diabetes/metabolism research and reviews. 2019 Sep;35(6):e3158.
8. Ke C, Narayan KV, Chan JC, Jha P, Shah BR. Pathophysiology, phenotypes and management of type 2 diabetes mellitus in Indian and Chinese populations. Nature Reviews Endocrinology. 2022 Jul;18(7):413-32.
9. Khan MA, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes–global burden of disease and forecasted trends. Journal of epidemiology and global health. 2020 Mar;10(1):107.
10. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, Hirsch IB, McDonnell ME, Molitch ME, Murad MH, Sinclair AJ. Treatment of diabetes in older adults: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2019 May;104(5):1520-74.
11. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. The Lancet. 2022 Jan 22.
12. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes–state-of-the-art. Molecular metabolism. 2021 Apr 1;46:101102.
13. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, Tunnicliffe D, Ruospo M, Natale P, Saglimbene V, Nicolucci A. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2021 Jan 13;372.
14. Quast DR, Schenker N, Menge BA, Nauck MA, Kapitza C, Meier JJ. Effects of lixisenatide versus liraglutide (short- and long-acting GLP-1 receptor agonists) on esophageal and gastric function in patients with type 2 diabetes. Diabetes Care. 2020 Sep 1;43(9):2137-45.
15. Reed J, Bain S, Kanamarlapudi V. A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, Metabolic Syndrome and Obesity. 2021 Aug 10:3567-602.
16. Riddle MC, Aronson R, Home P, Marre M, Niemoeller E, Miossec P, Ping L, Ye J, Rosenstock J. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes care. 2013 Sep 1;36(9):2489-96.

17. Riddle MC, Forst T, Aronson R, Sauque-Reyna L, Souhami E, Silvestre L, Ping L, Rosenstock J. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes care. 2013 Sep 1;36(9):2497-503.
18. Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, Cheng X, Zhou T, Niemoeller E, Souhami E, Davies M. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016 Nov 1;39(11):2026-35.
19. Rosenstock J, Diamant M, Aroda VR, Silvestre L, Souhami E, Zhou T, Perfetti R, Fonseca V, LixiLan PoC Study Group. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan proof-of-concept randomized trial. Diabetes Care. 2016 Sep 1;39(9):1579-86.
20. Seino Y, Min KW, Niemoeller E, Takami A, EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes, Obesity and Metabolism. 2012 Oct;14(10):910-7.
21. Tinajero MG, Malik VS. An update on the epidemiology of type 2 diabetes: a global perspective. Endocrinology and Metabolism Clinics. 2021 Sep 1;50(3):337-55.
22. Werner U, Haschke G, Herling AW, Kramer W. Pharmacological profile of lixisenatide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. Regulatory peptides. 2010 Sep 24;164(2-3):58-64.
23. Yang W, Min K, Zhou Z, Li L, Xu X, Zhu D, Venkateshwar Rao A, Murthy LS, Zhang N, Li I, Niemoeller E. Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: The GetGoal-L-C randomized trial. Diabetes, Obesity and Metabolism. 2018 Feb;20(2):335-43.