Efficacy and Safety of Ultra-rapid Lispro Insulin in Managing Type-1 and Type-2 Diabetes: A Systematic Review and Meta-Analysis

Deep Dutta, Lakshmi Nagendra[1], Saptarshi Bhattacharya[2], Meha Sharma[3]

Departments of Endocrinology and [3]Rheumatology, Center for Endocrinology, Diabetes, Arthritis and Rheumatism (CEDAR) Super-speciality Healthcare, Dwarka, Delhi, [1]Department of Endocrinology, JSS Academy of Higher Education and Research, Mysore, Karnataka, [2]Department of Endocrinology, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi, India

Abstract

Background: Mechanistically, subcutaneous ultra-rapid lispro (URLi) is faster than lispro. Whether this translates into a better post-prandial glucose (PPG) and glycemic control in type-1 diabetes (T1DM) and type-2 diabetes (T2DM) is unclear. Hence, we undertook this meta-analysis. **Methods:** Databases were searched for randomized controlled trials (RCTs) involving patients with T1DM/T2DM receiving URLi in intervention-arm, and placebo/prandial insulin as control. The primary outcome was a change in PPG. Secondary outcomes were alterations in glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), time in range (TIR), and adverse events. **Results:** Data from six RCTs (3687 patients) were analyzed. Lispro was the control arm in all RCTs. T1DM patients receiving mealtime URLi had lower HbA1c [mean difference (MD) −0.07%; 95% confidence interval (CI): −0.12 to − 0.01; $P = 0.02$; $I^2 = 42\%$] and 1-h PPG [MD − 1.18 mmol/L; 95% CI: −1.91 to − 0.44; $P = 0.002$; $I^2 = 100\%$]. T1DM patients receiving post-meal URLi had comparable HbA1c [MD 0.07%; 95% CI: −0.01 to 0.15; $P = 0.07$; $I^2 = 55\%$] and 1-h PPG [MD 0.22 mmol/L; 95% CI: −0.80 to 1.24; $P = 0.67$; $I^2 = 100\%$). T1DM patients on pumps receiving URLi had comparable TIR [MD 1.70; 95% CI: −0.29 to 3.69; $P = 0.09$; $I^2 = 98\%$], lower time in blood glucose <3 mmol/L with increased infusion-set reactions. T2DM patients receiving mealtime URLi had lower 1-h PPG [MD − 0.66 mmol/L; 95% CI: −0.69 to − 0.63; $P < 0.00001$; $I^2 = 0\%$(LH), 2-h-PPG [MD − 0.96 mmol/L; 95% CI: −1.00 to − 0.92; $P < 0.00001$; $I^2 = 0\%$], higher FPG [MD 0.18 mmol/L; 95% CI: 0.11–0.24; $P < 0.00001$; $I^2 = 20\%$], and higher HbA1c [MD 0.07%; 95% CI: −0.06 to 0.08; $P < 0.00001$; $I^2 = 0\%$]. **Conclusion:** Pre-meal URLi is better than lispro with regard to PPG control. Post-meal URLi is as good as lispro for PPG control. Post-meal URLi is inferior to pre-meal URLi for PPG control.

Keywords: Diabetes, efficacy, insulin, lispro, safety, ultra-rapid lispro

Introduction

Development of insulin analogues that closely mimic physiologic insulin release in response to a meal has been an important breakthrough in perfecting the action of exogenous insulin administration since its discovery 100 years ago. In spite of several significant advances and the availability of newer insulin analogues, a large number of people living with diabetes still fail to achieve optimal glycemic targets.[1]

A major limitation of regular insulin for post-prandial glycemic control is the delayed onset of action compared to the rapid post-meal glucose absorption, leading to a mismatch between plasma glucose peak and insulin effect.[2] The time lag between the release of injected insulin from the subcutaneous tissue and its absorption into the capillaries delays the onset of insulin action. This spurred the development of rapid-acting insulin (RAI) analogues that are released quickly into the capillaries following injection and thus have a faster onset of action.

Supplementary material available online

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_225_23

Address for correspondence: Dr. Deep Dutta, Center for Endocrinology, Diabetes, Arthritis and Rheumatism (CEDAR) Super-Speciality Healthcare, Dwarka, New Delhi - 110075, India. E-mail: deepdutta2000@yahoo.com

Submitted: 30-May-2023 **Revised:** 26-Jul-2023
Accepted: 25-Oct-2023 **Published:** 11-Jan-2024

How to cite this article: Dutta D, Nagendra L, Bhattacharya S, Sharma M. Efficacy and safety of ultra-rapid lispro insulin in managing type-1 and type-2 diabetes: A systematic review and meta-analysis. Indian J Endocr Metab 2023;27:467-75.

Conventional human regular insulin should be injected 30 min before meals. RAI analogues having a faster onset of action, such as lispro, aspart, and glulisine, can be injected 10–15 min before food.[2,3] An unmet need with RAI analogues is if the food intake is inadequate, the risk of post-prandial hypoglycaemia is aggravated. Also, if injected too close to the meals, the risk of post-prandial hyperglycaemia followed by hypoglycaemia persists. In extremes of ages such as toddlers and elderly, such mismatch can be especially troublesome.[3] Newer analogues such as fast-acting insulin aspart (FIAsp) and ultra-rapid lispro (URLi) can be injected from the beginning till 15–20 min after starting the meal by virtue of faster onset of action. They were approved for clinical use by the United States Food and Drug Administration (USFDA) in 2017 and 2020, respectively.[4]

We recently published a meta-analysis that demonstrated the superiority of FIAsp over insulin aspart in controlling post-prandial glucose (PPG) without increasing the risk of hypoglycaemia in insulin pump users.[5] Randomized controlled trials (RCTs) have been published evaluating URLi in type-1 diabetes mellitus (T1DM) and type-2 diabetes mellitus (T2DM) as subcutaneous injections and in insulin pumps.[6,7] However, no meta-analysis has been published to date which has tried to holistically evaluate the efficacy and safety of URLi in T1DM and T2DM. We performed this meta-analysis to address this knowledge gap.

Methods

The meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[8] The predefined protocol has been registered in PROSPERO having a registration number CRD42023417688. All RCTs published till March 2023 were considered. The meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the filled checklist of which can be found at the end of the manuscript.[8] Since ethical approval already exists for the individual studies included in the meta-analysis, no separate approval was required.

The PICOS criteria were used to screen and select the studies. Studies assessing people with T1DM and T2DM only were included. Studies that included participants with other varieties of diabetes were excluded. Trials with at least two treatment arms, with one of the groups on URLi either alone or as a part of a standard diabetes regimen, and the other group receiving either placebo or any other prandial insulin were included.

The primary outcome was to evaluate changes in PPG. Secondary outcomes were to evaluate changes in glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), percentage of people achieving HbA1c <7%, time in range (TIR), total daily insulin dose (TDID), basal and bolus insulin doses, discontinuation of medication due to adverse events, serious adverse events (SAE), treatment-emergent adverse events (TAE), hypoglycaemia, and any adverse events as described by authors. Outcomes of patients with T1DM and T2DM were analyzed and have been presented separately.

A detailed electronic database of Medline (Via PubMed), Embase (via Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL), ctri.nic.in, clinicaltrials.gov, global health, and Google Scholar were searched using a Boolean search strategy: (ultra-rapid lispro [MESH]) OR (URLi) or (lispro) AND (diabetes).

Data extraction with regard to all the primary and secondary outcomes stated above was carried out independently by two authors. Multiple publications from the same group on the same cohort of patients were pooled together and considered as a single study. Details have been elaborated in previous meta-analyses published by our group.[9] The risk of bias assessment was done by three authors using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 software. The different types of bias looked for have been elaborated in previous meta-analyses by our group.[9]

The international system of units (SI units) was used for all the analyses done. Continuous variable outcomes were presented as mean differences (MD). For dichotomous variables, outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI) and as hazard ratios (HR) for adverse events. RevMan 5.4 was used for doing all the statistical analysis and generation of Forest plots. A random effect model was used for analysis expressed as a 95% confidence interval (95% CI). The forest plot generated for all the different outcomes was used to assess the heterogeneity. We specifically used the χ^2 test on $N - 1$ degrees of freedom, with an alpha of 0.05 used for statistical significance with the I^2 test.[10] The details of heterogeneity analysis have been elaborated elsewhere.[9]

Grading of results is important as it helps to understand the quality of the results generated. After all any meta-analysis can be as good as the quality of RCTs used in the analysis. The grading/certainty of the evidence of some of the major outcomes was done using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[11,12] The details have been elaborated elsewhere.[9] Publication bias was assessed by plotting the funnel plot.[12] The details of how the funnel plots were charted have been elaborated elsewhere.[9] The funnel plots of the key outcomes of this study have been elaborated in supplementary figures. Table 2 was generated using the GRADE software (https://gdt.gradepro.org/app/) which highlights the grading of key outcomes.

Results

A total of 65 articles were found after the initial search [Figure 1]. Sixteen duplicate studies were removed. After the screening of the titles and abstracts, followed by full-texts, the search was reduced to 29 studies which were evaluated in detail for inclusion in this meta-analysis [Figure 1]. Finally, six RCTs (3687 patients with diabetes) that fulfilled all criteria were analyzed in this meta-analysis.[6,7,13-16]

Table 1: Characteristics of patients in the different randomized controlled trials evaluated in this meta-analysis

	Age (years)	Male (%)	Type of diabetes	Duration of diabetes, years	BMI kg/m²	Baseline HbA1c (%)
Klaff *et al*.[6]						
Mealtime URLi (*n*=451)	44.1±13.7	55.4	T1DM	18.8±12.3	26.6±4.2	7.34±0.65
Mealtime lispro (*n*=442)	44.5±13.6	57.9		19.1±12.0	26.4±4.3	7.33±0.67
Post-meal URLi (*n*=329)	44.5±14.3	55.3		18.8±11.7	26.7±4.6	7.36±0.64
Wadwa *et al*.[14]						
Mealtime URLi (*n*=280)	12.10±3.42	48.6	T1DM	4.5±3.58	20.5±4.6	7.81±0.87
Mealtime lispro (*n*=298)	12.39±3.18	53		4.7±3.28	20.3±4.19	7.81±0.91
Post-meal URLi (*n*=138)	12.32±3.75	52.9		4.6±3.32	20.5±4.39	7.77±0.85
Warren *et al*.[15]						
URLi (*n*=215)	48.2±15.4	44.2	T1DM	25.9±12.6	27±4	7.56 (0.59)
Lispro (*n*=217)	44.7±14.9	45.2		25.4±13.2	27.2±4.1	7.54±0.58
Bode *et al*.[13]						
Overall (*n*=49)	39.6±11.7	46.9	T1DM	21.3±12.1	26.9±3.8	7.06±0.68
Blevins *et al*.[7]						
Mealtime URLi (*n*=336)	60.2±9.4	54.8	T2DM	16.4±7.8	32.1±5.7	7.27±0.68
Mealtime lispro (*n*=337)	61.0±9.2	51.9		16.6±7.9	32.4±5.8	7.31±0.72
Zhou *et al*.[16]						
Mealtime URLi (*n*=395)	58.3±9.3	53.9	T2DM	13.91±7.03	27.09±3.78	7.73±0.87
Mealtime lispro (*n*=200)	58.7±9.5	53.5		13.86±6.72	27.09±3.56	7.78±0.88

BMI: Body mass index; T1DM : Type-1 diabetes mellitus; T2DM : Type-2 diabetes mellitus, URLi: Ultra-rapid lispro

Of the six RCTs included in this meta-analysis, a subgroup analysis was done based on the type of diabetes. A total of four studies evaluated the safety and efficacy of URLi vs. lispro in T1DM.[6,13-15] Of the four studies, two studies evaluated mealtime URLi vs. lispro and post-meal URLi (administered up to 20 min after the start of a meal) vs. lispro in T1DM.[6,14] Two studies evaluated URLi vs. lispro use in insulin pumps in T1DM.[13,15] Two studies evaluated the safety and efficacy of mealtime URLi vs. lispro in T2DM.[7,16] Both these studies used stable doses of metformin and/or sodium-glucose transport inhibitors (SGLT2i) during the study.[7,16] The details of the studies have been elaborated in Table 1. The summaries of the risk of bias of the six studies have been elaborated in Figure 2.

Effect of Ultra-Rapid Lispro on Primary and Secondary Outcomes

Type-1 diabetes mellitus

Mealtime URLi vs. Lispro

Data from two studies involving 1471 people with T1DM was analyzed to find out the impact of mealtime URLi on primary and secondary outcomes after 26 weeks of treatment. As compared to lispro, patients receiving mealtime URLi had significantly lower HbA1c at 26 weeks [MD − 0.07% (95% CI: −0.12 to − 0.01); P = 0.02; I^2 = 42% (moderate heterogeneity (MH)); high certainty of evidence (HCE)); Figure 3a]. At 26 weeks, 1-h PPG excursion was significantly lower in patients receiving mealtime URLi as compared to lispro [MD − 1.18 mmol/L (95% CI: −1.91 to − 0.44); P = 0.002; I^2 = 100% (high heterogeneity (HH); low certainty of evidence (LCE); Figure 3b]. Percentage of participants achieving HbA1c <7% was comparable between the groups [OR 1.15 (95% CI: 0.92–1.45); P = 0.21; I^2 = 0% (LH); Figure 3c]. The occurrence of deaths [OR 0.98 (95% CI: 0.06–15.72); P = 0.99; I^2 = 0%], SAE [OR 0.79 (95% CI: 0.52–1.21); P = 0.29; I^2 = 0% (LH); HCE; Figure 3d], and TAEs [OR 0.95 (95% CI: 0.07–12.25); P = 0.97; I^2 = 97% (HH)] was comparable between the groups.

Post-meal URLi vs. Lispro

Data from two studies involving 1207 people with T1DM was analyzed to find out the impact of post-meal URLi on primary and secondary outcomes after 26 weeks of treatment. As compared to lispro, patients receiving post-meal URLi had comparable HbA1c at 26 weeks [MD 0.07% (95% CI: −0.01 to 0.15); P = 0.07; I^2 = 55% (MH); HCE; Figure 4a]. At 26 weeks, 1-h PPG excursion was comparable in patients receiving post-meal URLi as compared to lispro [MD 0.22 mmol/L (95% CI: −0.80 to 1.24); P = 0.67; I^2 = 100% (HH); LCE; Figure 4b]. Percentage of participants achieving HbA1c <7% was significantly lower in the post-meal URLi group compared to the lispro group [OR 0.74 (95% CI: 0.57–0.97); P = 0.03; I^2 = 0% (LH); Figure 4c]. The occurrence of death [OR 0.45 (95% CI: 0.02–11.0); P = 0.62], SAE [OR 0.72 (95% CI: 0.44–1.19); P = 0.20; I^2 = 0% (LH); HCE; Figure 4d], and TAE [OR 0.96 (95% CI: 0.73–1.27); P = 0.77; I^2 = 0% (LH)] was comparable between the groups.

URLi vs. lispro in pumps

Data from two studies involving 525 people with T1DM was analyzed to find out the impact of URLi in insulin pumps on primary and secondary outcomes after 12–16 weeks of treatment. As compared to lispro, patients receiving URLi had a comparable percentage of TIR 3.9–10 mmol/L [MD 1.70% (95% CI: −0.29 to 3.69); P = 0.09; I^2 = 98% (HH); Figure 5a] and time below range <3.9 mmol/L [MD − 0.61% (95% CI: −1.36 to 0.13); P = 0.11; I^2 = 99% (HH); Figure 5b].

Table 2: Summary of findings of the key outcomes of this meta-analysis comparing ultra-rapid lispro insulin to lispro insulin

Certainty assessment							No. of patients		Effect		Certainty importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	URLi	Lispro	Relative (95% CI)	Absolute (95% CI)	
Mealtime (pre-meal) URLi compared to lispro in type-1 diabetes											
HbA1C (%) at week 26											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	731	740	–	MD 0.07 lower (0.11 lower to 0.03 lower)	⊕⊕⊕⊕ High
1-hour post-prandial glucose excursion at week 26 (1 h)											
2	Randomized trials	Not serious	Serious	Not serious	Not serious	Publication bias	731	740	–	MD 1.4 lower (1.42 lower to 1.38 lower)	⊕⊕◯◯ Low
Serious adverse events											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	42/731 (5.7%)	52/740 (7.0%)	OR 0.79 (0.52 to 1.21)	14 fewer per 1000 (from 32 fewer to 14 more)	⊕⊕⊕⊕ High
Mealtime (pre-meal) URLi compared lispro in type-2 diabetes											
HbA1C (%) at week 26											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	642	499	–	MD 0.07 higher (0.06 higher to 0.08 higher)	⊕⊕⊕⊕ High
Post-prandial glucose excursion at week 26 (1 h)											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	642	499	–	MD 0.66 lower (0.69 lower to 0.63 lower)	⊕⊕⊕⊕ High
Serious adverse events											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	59/731 (8.1%)	40/537 (7.4%)	OR 1.08 (0.71 to 1.65)	5 more per 1000 (from 20 fewer to 43 more)	⊕⊕⊕⊕ High
Post-meal URLi compared to Lispro in type-1 diabetes											
HbA1C (%) at week 26											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	467	740	–	MD 0.08 higher (0.04 higher to 0.13 higher)	⊕⊕⊕⊕ High
Post-prandial glucose excursion at week 26 (1 h)											
2	Randomized trials	Not serious	Serious	Not serious	Not serious	Publication bias	467	740	–	MD 0.56 higher (0.54 higher to 0.59 higher)	⊕⊕◯◯ Low
Serious adverse events											
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	26/467 (5.6%)	52/740 (7.0%)	OR 0.71 (0.43 to 1.16)	19 fewer per 1,000 (from 39 fewer to 10 more)	⊕⊕⊕⊕ High

OR: Odds ratio; URLi: ultra-rapid lispro insulin; T1DM: type-1 diabetes; T2DM: type-2 diabetes; MD: mean difference; CI: confidence interval

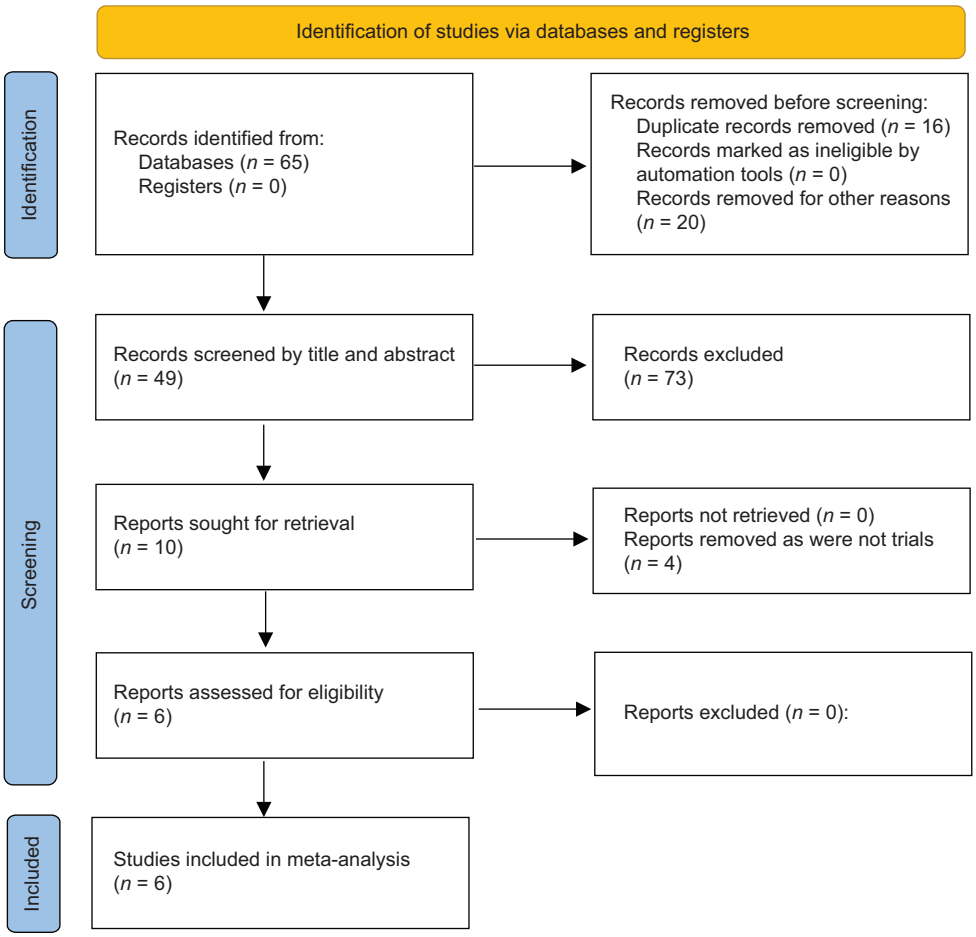


Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis

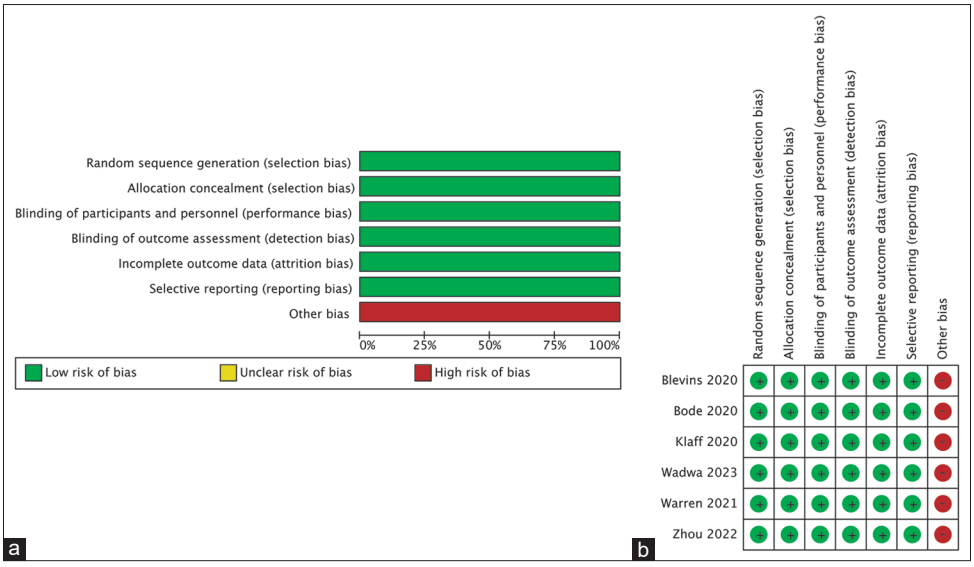


Figure 2: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study

However, the percentage of time below range <3 mmol/L was significantly lower in the URLi group as compared to the lispro group [MD − 0.39% (95% CI: −0.63 to − 0.14); P = 0.002; I^2 = 99% (HH); Figure 5c].

There were no deaths in both groups during the study period. The occurrence of premature infusion-set changes [OR 1.59 (95% CI: 1.12–2.27); P = 0.01; I^2 = 0% (LH)], infusion-set reactions [OR 5.71 (95% CI: 2.11–15.49); P = 0.0006; I^2 = 28% (LH);

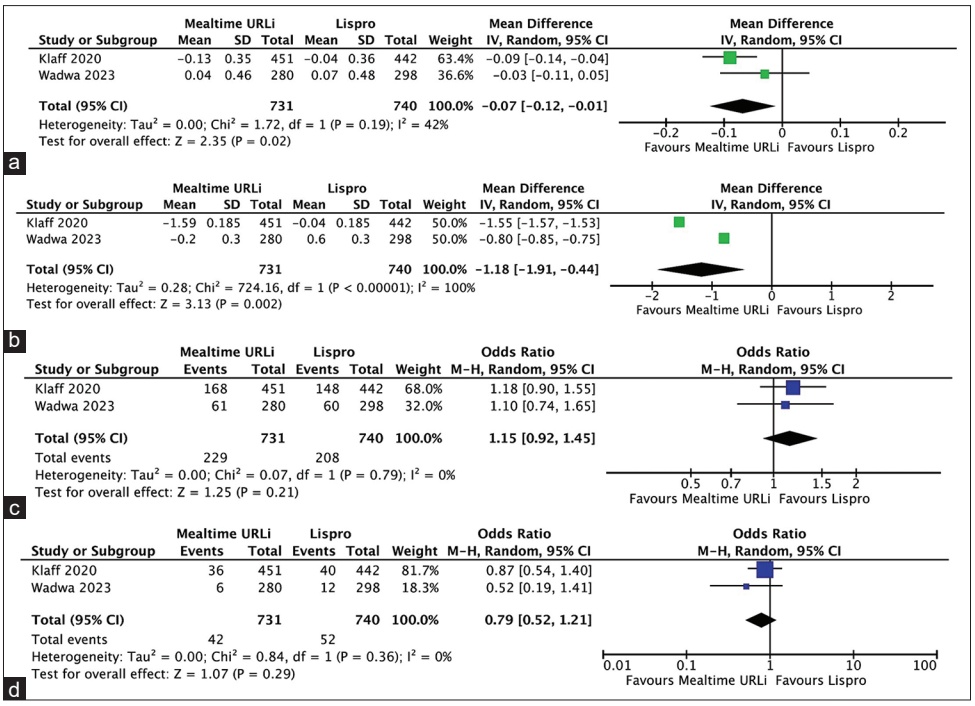


Figure 3: Forest plot highlighting the impact of mealtime URLi as compared to lispro, after 26 weeks of therapy in T1DM on (a) HbA1c; (b) 1-h PPG excursion; (c) Percent of people achieving HbA1c <7%; (d) Serious adverse events

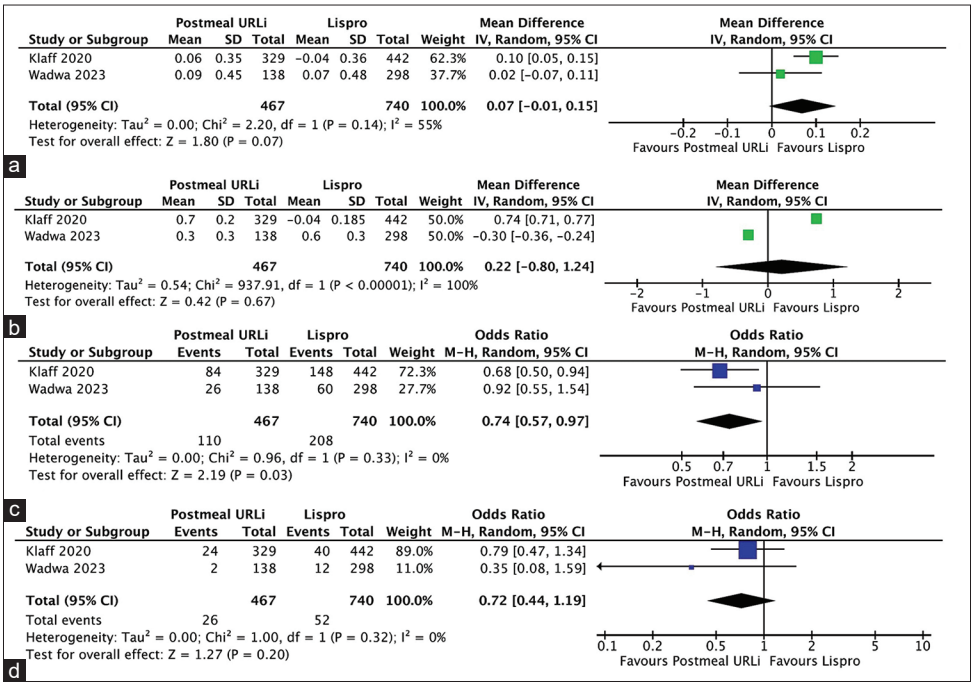


Figure 4: Forest plot highlighting the impact of post-meal URLi as compared to lispro, after 26 weeks of therapy in T1DM on (a) HbA1c; (b) 1-h PPG excursion; (c) Percent of people achieving HbA1c <7%; (d) Serious adverse events

Figure 5d], TAE [OR 2.45 (95% CI: 1.20 – 4.99); $P = 0.01$; $I^2 = 54\%$ (LH); Figure 5e] were significantly higher in the URLi group. This was reported to be majorly driven by an increase in infusion-set reactions, over 90% of which were deemed mild. The occurrence of pump occlusion alarms [OR 0.89 (95% CI: 0.52–1.50); $P = 0.45$; $I^2 = 0\%$ (LH)], unexplained hyperglycaemia [OR 0.73 (95% CI: 0.33–1.61); $P = 0.44$; $I^2 = 59\%$ (LH)], infusion-set problems [OR 1.18 (95% CI: 0.83–1.69); $P = 0.36$; $I^2 = 0\%$ (LH)], and SAE [OR 1.44 (95% CI: 0.63–3.31); $P = 0.39$; $I^2 = 0\%$ (LH), Figure 5f] was comparable between both the groups.

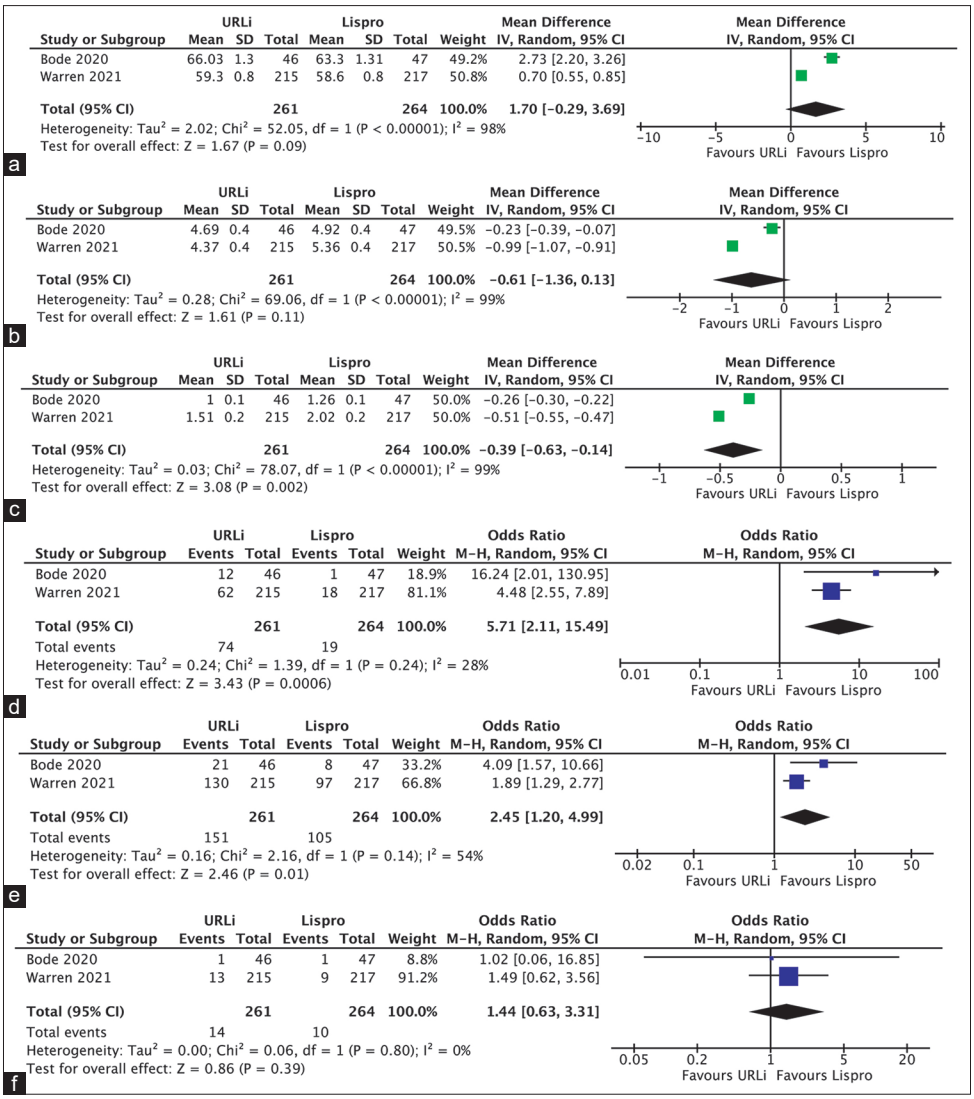


Figure 5: Forest plot highlighting the impact of URLi as compared to lispro in insulin pumps after 12–16 weeks of therapy in T1DM on (a) Percent time in range 3.9–10 mmol/L; (b) Percent time <3.9 mmol/L; (c) Percent time <3 mmol/L; (d) Infusion-set reactions; (e) Treatment-emergent adverse events; (f) Serious adverse events

Mealtime URLi vs. lispro in type-2 diabetes mellitus

Data from two studies involving 1141 people with T2DM was analyzed to find out the impact of mealtime URLi on primary and secondary outcomes after 26 weeks of treatment. As compared to lispro, patients receiving mealtime URLi had a significantly higher HbA1c [MD 0.07% (95% CI: −0.06 to 0.08); $P < 0.00001$; $I^2 = 0\%$ (LH); HCE; Figure 6a]. At 26 weeks, 1-h PPG excursion [MD − 0.66 mmol/L (95% CI: −0.69 to − 0.63); $P < 0.00001$; $I^2 = 0\%$ (LH); HCE; Figure 6b] and 2-h PPG excursion [MD − 0.96 mmol/L (95% CI: −1.00 to − 0.92); $P < 0.00001$; $I^2 = 0\%$ (LH); HCE; Figure 6c] was lower in patients receiving post-meal URLi as compared to lispro. Fasting plasma glucose was significantly higher in patients receiving mealtime URLi as compared to lispro [MD 0.18 mmol/L (95% CI: 0.11–0.24); $P < 0.00001$; $I^2 = 20\%$ (LH); Figure 6d]. The occurrence of deaths [OR 0.74 (95% CI: 0.07–8.03); $P = 0.80$; $I^2 = 32\%$ (LH)], SAE [OR 1.08 (95% CI: 0.71–1.65); $P = 0.72$; $I^2 = 0\%$ (LH); HCE; Figure 6e], and TAE [OR 1.07 (95% CI: 0.85–1.35); $P = 0.54$; $I^2 = 0\%$ (LH); Figure 6f] was comparable between the groups. MD in insulin doses was not analyzed as there was no baseline data on the same provided in the published RCTs.

The key summary of findings of the study focussing on the glycaemic outcomes after 26 weeks of therapy and the side effect profile has been elaborated in Table 2. Funnel plots were plotted to evaluate the presence of publication bias, and have been elaborated in Supplementary Figure 1.

Discussion

URLi is a modification of human insulin lispro, containing two enabling excipients, citrate and treprostinil, that accelerate insulin absorption beyond that achieved by lispro. Faster onset of action of URLi more closely mimics physiologic insulin

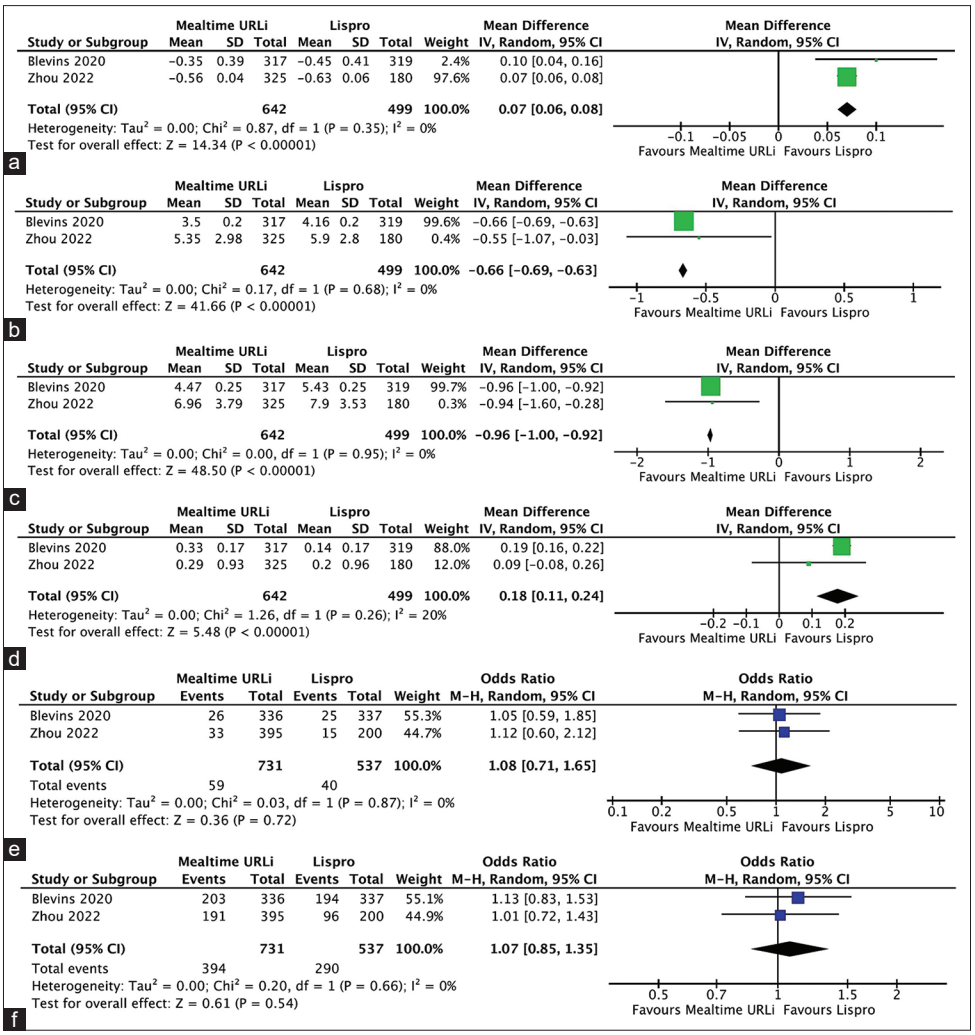


Figure 6: Forest plot highlighting the impact of post-meal URLi as compared to lispro, after 26 weeks of therapy in T2DM on (a) HbA1c; (b) 1-h PPG excursion; (c) 2-h PPG excursion; (d) Fasting plasma glucose; (e) Serious adverse events; (f) Treatment-emergent adverse events

rise after food.[17] The citrate injected into subcutaneous tissue causes a localized increase in vascular permeability, whereas treprostinil induces localized vasodilation leading to accelerated insulin absorption.[18] A pooled analysis of the pharmacokinetic and pharmacodynamic data of URLi across different population groups showed that URLi has a 5-min faster onset of appearance in serum, an eight-fold greater exposure in the first 15 min, along with a 43% reduction in exposure beyond 3 h compared to insulin lispro.[19] Comparison of pharmacokinetics and pharmacodynamics of URLi, FIAsp, lispro, and aspart insulins revealed that URLi has the fastest insulin absorption, the greatest early insulin exposure, lowest late insulin exposure, and greatest 2 h post-prandial blood glucose lowering.[4] This results in a post-prandial 0–3 h glucose excursion with URLi being very close to that of healthy individuals, and better than any of the other three peer short-acting insulins.[4]

This is the first meta-analysis to holistically evaluate the pre-meal and post-meal URLi data in the management of T1DM and T2DM as compared to lispro. Our analysis shows that subcutaneous mealtime URLi is superior to mealtime lispro with regard to 1-h PPG control in T1DM. However, when administered post-meal, URLi lost this superiority and had comparable 1-h PPG lowering compared to mealtime lispro. This provides reassuring data that the glycemic efficacy is not compromised when URLi is administered post-meal when compared to pre-meal lispro insulin. Better PPG control with URLi in T1DM did not come at an increased cost of hypoglycaemia and other side effects. However, it must be realized that the better 1-h PPG control with URLi in T1DM did not translate into a clinically meaningful lowering of HbA1c or more percentage of patients achieving HbA1c <7%. When used in insulin pumps, URLi had similar TIR compared to lispro with an added advantage of significantly reduced occurrence of severe hypoglycaemia. However, injection site reactions, though mild, were much more common with URLi as compared to lispro. The reason for this is not known and needs further evaluation. Whether the two enabling excipients, citrate and Treprostinil, in URLi are responsible for injection site reactions needs further evaluation as such reactions have

not been seen with lispro insulin. No such reactions were noted with Fiasp in insulin pumps in a prior meta-analysis.[9] Fiasp in the pump was noted to be superior to aspart insulin with regard to PPG control in that meta-analysis.[9] Currently, the two fastest short-acting insulin analogues available are URLi and FIAsp. However, a head-to-head comparison between the two has not been done to date, hence remains an area for future research.

The good clinical practice suggestions from this meta-analysis are that subcutaneous lispro insulin can be switched to subcutaneous URLi in T1DM when we want to give post-meal bolus insulin. Also, when PPG control with lispro is suboptimal, switching over to URLi can be considered; however, in this scenario, pre-meal URLi should be preferred over post-meal URLi.

In T2DM, subcutaneous URLi was found to be superior to subcutaneous lispro with regard to 1-h and 2-h PPG control. However, the better PPG control did not translate into a HbA1c reduction, or a greater percentage of patients achieving HbA1c <7%. Hence, switching to URLi from subcutaneous lispro insulin can be considered in T2DM, only when PPG control with lispro becomes challenging. Dedicated RCTs evaluating post-meal URLi in T2DM are lacking and hence are urgently warranted. Also, URLi in insulin pump has not been evaluated in T2DM.

Limitations of this meta-analysis include that for most of the outcomes, data was available from two RCTs for analysis as different studies evaluated different aspects of URLi use (pre-meal or post-meal administration; subcutaneous or insulin pumps) in T1DM and T2DM. Current available data from RCTs with regard to the use of subcutaneous URLi are limited to 26 weeks in T1DM and T2DM; and only 12–16 weeks when used in insulin pump. Hence long-term glycaemic durability and safety data are lacking. Hence an urgent need remains for larger multicentric studies with a longer duration of follow-up of more than a year with regard to the use of URLi insulin in T1DM and T2DM.

To conclude, subcutaneous URLi injected before meals is more effective than lispro in controlling PPG both in T1DM and T2DM. This meta-analysis also highlights that the current data is not strong enough to recommend routine switching of lispro to URLi. As per current evidence, the use of URLi was not associated with improvement in HbA1c in T2DM. URLi should be considered only in those who are having challenges with controlling post-prandial hyperglycaemia with greater glycemic variability with lispro. URLi can be an option when we want to administer post-meal boluses in T1DM but data on the same in people with T2DM is lacking.

Financial support and sponsorship

Nil.

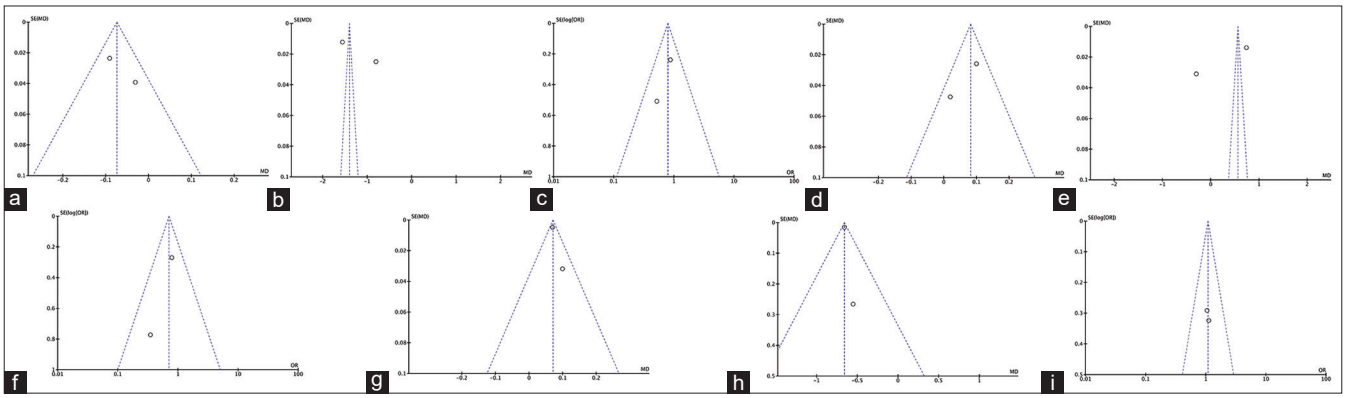
Conflicts of interest

There are no conflicts of interest.

References

1. Datye KA, Boyle CT, Simmons J, Moore DJ, Jaser SS, Sheanon N, *et al*. Timing of meal insulin and its relation to adherence to therapy in type 1 diabetes. J Diabetes Sci Technol 2018;12:349-55.
2. Martens TW, Bergenstal RM, Pearson T, Carlson AL, Scheiner G, Carlos C, *et al*. Making sense of glucose metrics in diabetes: linkage between postprandial glucose (PPG), time in range (TIR) and hemoglobin A1c (A1C). Postgrad Med 2021;133:253-64.
3. Dutta D, Khandelwal D, Kalra S. Injectable combination therapies for the management of diabetes: An Indian perspective. Expert Opin Drug Metab Toxicol 2020;16:209-16.
4. Heise T, Piras de Oliveira C, Juneja R, Ribeiro A, Chigutsa F, Blevins T. What is the value of faster acting prandial insulin? Focus on ultra rapid lispro. Diabetes Obes Metab 2022;24:1689-701.
5. Dutta D, Mohindra R, Mahajan K, Sharma M. Performance of fast-acting aspart insulin as compared to aspart insulin in insulin pump for managing type 1 diabetes mellitus: A meta-analysis. Diabetes Metab J 2023;47:72-81.
6. Klaff L, Cao D, Dellva MA, Tobian J, Miura J, Dahl D, *et al*. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study. Diabetes Obes Metab 2020;22:1799-807.
7. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM; PRONTO-T2D Investigators. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. Diabetes Care 2020;43:2991-8.
8. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi: 10.1136/bmj.d5928.
9. Dutta D, Agarwal A, Maisnam I, Singla R, Khandelwal D, Sharma M. Efficacy and safety of the novel dipeptidyl peptidase-4 inhibitor gemigliptin in the management of type 2 diabetes: A meta-analysis. Endocrinol Metab (Seoul) 2021;36:374-87.
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and metaanalyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009;339:b2700.
11. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
12. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess 2000;4:1–115.
13. Bode BW, Garg SK, Norwood P, Morales C, Hardy T, Liu R, *et al*. Compatibility and safety of ultra rapid lispro with continuous subcutaneous insulin infusion in patients with type 1 diabetes: PRONTO-pump study. Diabetes Technol Ther 2021;23:41-50.
14. Wadwa RP, Laffel LM, Franco DR, Dellva MA, Knights AW, Pollom RK. Efficacy and safety of ultra-rapid lispro versus lispro in children and adolescents with type 1 diabetes: The PRONTO-Peds trial. Diabetes Obes Metab 2023;25:89-97.
15. Warren M, Bode B, Cho JI, Liu R, Tobian J, Hardy T, *et al*. Improved postprandial glucose control with ultra rapid lispro versus lispro with continuous subcutaneous insulin infusion in type 1 diabetes: PRONTO-Pump-2. Diabetes Obes Metab 2021;23:1552-61.
16. Zhou J, Chen S, Cheng J, Zhu J, Lou Y, Bao Y, *et al*. Ultra rapid lispro improves postprandial glucose control versus lispro in combination with insulin glargine/degludec in adults with type 2 diabetes: A prospective, randomized, double-blind, phase 3 trial. Sci Bull (Beijing) 2022;67:1785-91.
17. Pratt E, Leohr J, Heilmann C, Johnson J, Landschulz W. Treprostinil causes local vasodilation, is well tolerated, and results in faster absorption of insulin Lispro. Diabetes 2017;66:A253.
18. Moyers JS, Zhang C, Siesky AM, Cox AL, Sperry AE, Hansen RJ, *et al*. Exploration of the mechanism of accelerated absorption for a novel insulin Lispro formulation. Diabetes 2017;66:A250.
19. Leohr J, Dellva MA, Carter K, LaBell E, Linnebjerg H. Ultra rapid Lispro (URLi) accelerates insulin Lispro absorption and insulin action vs Humalog(®) consistently across study populations: A pooled analysis of pharmacokinetic and Glucodynamic data. Clin Pharmacokinet 2021;60:1423-34.

SUPPLEMENTARY FIGURE



Supplementary Figure 1: Funnel plot of all the included studies in the meta-analysis (assessing the publication bias) of the main outcomes assessed. (a) Impact of mealtime ultra-rapid lispro (URLi) vs. lispro on HbA1c at 26 weeks in type-1 diabetes (T1DM); (b) Impact of mealtime URLi vs. lispro on 1-h post-meal post-prandial glucose (PPG) excursions (mmol/L) at 26 weeks; (c) Impact of mealtime URLi vs. lispro on serious adverse events (SAEs) in T1DM; (d) Impact of post-meal URLi vs. lispro in T1DM; (e) Impact of post-meal URLi vs. lispro on 1-h post-meal PPG excursions (mmol/L) at 26 weeks; (f) Impact of mealtime URLi vs. lispro on SAEs in T1DM; (g) Impact of mealtime URLi vs. lispro on HbA1c at 26 weeks in type-2 diabetes (T2DM); (h) Impact of mealtime URLi vs. lispro on 1-h post-meal PPG excursions (mmol/L) at 26 weeks; (i) Impact of mealtime URLi vs. lispro on SAEs in T2DM