*Iran J Public Health, Vol. 53, No.2, Feb 2024, pp.313-322*

**Review Article**

# Efficacy and Safety of Insulin Degludec/Insulin Aspart versus Biphasic Insulin Aspart 30 in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials

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**(Received 19 Jun 2023; accepted 18 Sep 2023)**

**Abstract**

**Background:** We systematically reviewed and analyzed the efficacy and safety of insulin degludec/insulin aspart (IDegAsp) versus biphasic insulin aspart 30 (BIAsp 30) in patients with type 2 diabetes (T2D).

**Methods:** We used computers to search the Embase, PubMed, Clinical Trials, and the Cochrane Library database, and collected randomized controlled trials (RCTs) on the treatment of IDegAsp versus BIAsp 30 in T2D patients. The research period was from the establishment of the database to May 19, 2023. We used Review Manager 5.20 statistical software for systematic meta-analysis.

**Results:** We included 8 RCTs with 2281 participants. IDegAsp was better to BIAsp30 in improving fasting plasma glucose (FPG) levels ($P<0.001$) and reducing the endpoint daily average insulin dose ($P<0.01$). Furthermore, compared with BIAsp30, IDegAsp significantly reduced the risk of nocturnal hypoglycemic events ($P<0.001$). However, there was no significant difference in the improvement of body weight change ($P=0.99$), glycosylated hemoglobin ($P=0.50$), the overall risk of hypoglycemic events ($P=0.57$) and adverse events ($P=0.89$) between the two groups.

**Conclusion:** Compared with BIAsp30, IDegAsp could significantly reduce FPG levels, insulin dosage, and the risk of nocturnal hypoglycemic events in T2D patients, without increasing the overall risk of adverse events.

**Keywords:** Type 2 diabetes; Biphasic insulin aspart 30; Insulin degludec; Insulin aspart; Effectiveness; Meta-analysis; Randomised controlled trials

## Introduction

In recent years, with the improvement and enhancement of the global material life, the incidence rate of type 2 diabetes (T2D) and its complications continues to rise, which seriously affects people's life, health and safety (1). According to statistics, there will be 592 million people suffering from diabetes worldwide by 2035, of which T2D patients account for 77% of the total number (2). The harm of T2D to patients is not only physical, but also a major issue for their families and society (3).

The 2020 ADA guidelines for diagnosis and treatment of diabetes suggests that patients with significant hyperglycemia, glycosylated hemoglobin>10% or random blood glucose > 16.7 mmol/L should receive insulin treatment as soon as possible (4). For patients who require both basic insulin therapy and dietary insulin therapy, a two-dose premixed insulin regimen can be considered (5). However, the commonly used premixed insulin in clinical practice has drawbacks such as short action time, high blood glucose variability, uneven drug release concentration, and increased risk of hypoglycemia. Therefore, a safer and more effective new insulin formulation is needed in clinical practice.

Insulin degludec/insulin aspart (IDegAsp) is a new generation of long-acting basal insulin, which is Insulin degludec (IDeg) combined with insulin aspart (IAsp) (6). IDegAsp is a fully soluble insulin analogue compound formulation that has the advantages of long action time, low blood sugar variability, and no need for resuspension before injection (7). However, research evidence on the hypoglycemic efficacy and safety of IDegAsp is still insufficient.

Therefore, in the present study, we used a meta-analysis method to evaluate the efficacy and safety of IDegAsp versus biphasic insulin 30 (BIAsp30) in the treatment of T2D patients. We aimed to provide a reliable reference for the prevention and management of T2D.

## Methods

### *Literature retrieval strategy*

We searched 4 large databases using computers, including Embase, Pubmed, Clinical Trials, and the Cochrane Library database. The research period was from the date of database establishment to May 19, 2023. The keywords we searched include: "Randomised controlled trials (RCTs)", "Type 2 diabetes", "Biphasic insulin aspart 30", "Insulin degludec", "Insulin aspart". The literature we searched was limited to published articles with English. Our meta-analysis of RCTs was strictly conducted in accordance with PRISMA standards.

### *Inclusion and exclusion criteria*

The inclusion criteria included: 1) Published articles with English language; 2) The patient was clinically diagnosed with T2D; 3) The experimental group subjects used IDegAsp, while the control group subjects used BIAsp30; 4) RCTs. Exclusion criteria we used include: 1) Non clinical RCTs; 2) Not published in English; 3) Articles on case reports, meta-analyses, and reviews; 4) Publish articles with duplicate data; 5) Articles that could not accurately extract data or lack data; 6) Basic experimental research (animal and/or cell).

### *Data Extraction*

The general data extracted included the study country (region), interval period, category, and population. The information of participants included: gender, age, body weight, grouping, previous medical history, fasting plasma glucose (FPG), duration of diabetes, glycosylated hemoglobin (HbA1c), previous blood glucose control strategies, intervention measures, etc. In addition, we also collected relevant information for evaluating the quality of research and the risk of bias. All data extraction was independently selected by two researchers, including literature selection, data extraction, and cross-examination.

### *Quality Evaluation*

We used the Cochrane assessment tool to evaluate the data and bias risk of RCTs. The content of literature evaluation included: random sequence, allocation concealment, blinding of participants and outcomes, incomplete data, selective reports, and other (8). During this process, if there were any disagreements, both researchers would discuss and resolve the issue, or ask a third researcher to help make a judgment.

### *Obtained literature results*

Our analysis of the literature mainly included two aspects: drug efficacy and adverse reactions. The primary outcomes of our analysis were the evalu-

ation of the effectiveness of IDegAsp on FPG control and the change in the daily average insulin dose at the endpoint compared to BIAsp30. The secondary outcomes were the effect of IDegAsp on changes in body weight and HbA1c. Other outcomes included the impact of IDegAsp on the risk of nocturnal hypoglycemic events, overall risk of hypoglycemic events, and adverse events.

### *Statistical analysis*

We conducted a meta-analysis using RevMan 5.2 statistical software. We used relative risk (RR) as the influence quantity of the second categorical variable, mean difference (MD) as the influence quantity of continuous variables, and used 95% confidence interval (CI) to represent each effect quantity. We used $\chi^2$ to test and evaluate the heterogeneity of RCTs. We decided to use a fixed effects model ($P$>0.05, $I^2$ <50%) or a random effects model ($P$<0.1, $I^2$ >50%) based on the heterogeneity of RCTs. For publication bias evaluation, we used Begg's and Egger's tests. If $P$ < 0.05, it indicated publication bias.

## Results

### *Literature review and data retrieval*

We retrieved 1286 articles from 4 large databases, deleted 1061 duplicate articles, and obtained a total of 225 articles. Then, we excluded 146 articles by reading the title and abstract sections, leaving 23 articles. By reading the entire content, we excluded 15 articles that did not meet the inclusion criteria, of which 3 were published with duplicate data, 9 were not RCTs, and 3 were unable to obtain complete data. Finally, we obtained 8 articles for further meta-analysis (Fig. 1).

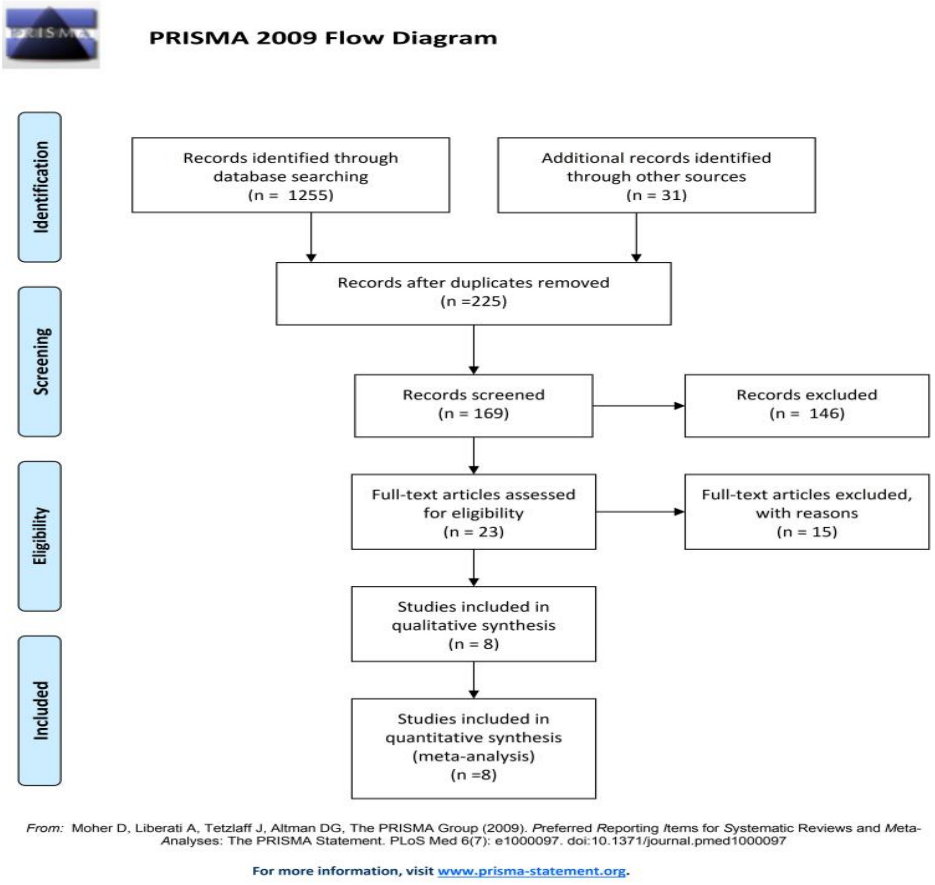


**Fig. 1:** Literature retrieval process and results

### *Characteristics and quality of included articles*

Among the 8 RCTs we included (9-16), 5 were multicenter studies (9-12, 14) and 3 were single center studies (13, 15, 16), totaling 2281 participants. Among these participants, there were 1302 patients in the IDegAsp group and 979 patients in the BIAsp 30 group (9-16). We summarized the relevant content and features of included RCTs in Table 1. Furthermore, to clarify the quality of our inclusion in RCTs, we used the Cochrane bias risk assessment tool. We found that the quality of all included RCTs was high and the risk of bias was low (Fig. 2).

**Table 1:** The basic characteristics of the 8 studies included in the meta-analysis

| *Study* | *Country* | *Population* | *IDegAsp patients* | *BIAsp 30 patients* | *Baseline doses* | | *Time of duration* | *Outcomes used in the meta-analysis* |
|---|---|---|---|---|---|---|---|---|
| | | | | | IDegAsp | BIAsp 30 | | |
| Niskanen L et al. 2012 (9) | Finland, France, Germany, Poland and Spain | Adults (y > 18 and y < 75) with type 2 diabetes | 61 | 62 | (0.14-0.16) U/kg | (0.14-0.16) U/kg | 16 Weeks | FPG, Insulin dose, Body weight, HbA1c, Nocturnal hydroglycemic events, Hypoglycaemic events, Adverse events |
| Fulcher GR et al. 2014 (10) | Australia, Denmark, Finland, India, Malaysia, Poland, Sweden, Taiwan, Thailand, and Turkey | Adults (y ≥ 18) with type 2 diabetes | 224 | 222 | 1.08 U/kg | 1.20 U/kg | 26 Weeks | FPG, Insulin dose, Body weight, HbA1c, Nocturnal hydroglycemic events, Hypoglycaemic events, Adverse events |
| Kaneko S et al. 2015(11) | Hong Kong, Japan, Malaysia, South Korea and Taiwan | Asian adults (y ≥ 18, and ≥ 20 for Japan and Taiwan) with type 2 diabetes | 282 | 142 | 0.79 U/kg | 0.99 U/kg | 26 Weeks | FPG, Insulin dose, Body weight, HbA1c, Nocturnal hydroglycemic events, Hypoglycaemic events, Adverse events |
| Franek E et al. 2016 (12) | Algeria, Bulgaria, Croatia, Czech Republic, Germany, Poland, Romania, Slovakia, Turkey and Ukraine | Adults (y ≥ 18) with type 2 diabetes | 197 | 197 | 0.80 U/kg | 0.82 U/kg | 26 Weeks | FPG, Insulin dose, Body weight, HbA1c, Nocturnal hydroglycemic events, Hypoglycaemic events, Adverse events |
| Onishi Y et al. 2017 (13) | Japan | Adults (y ≥ 20) with type 2 diabetes | 33 | 33 | (21.90-23.40) U | (22.10-25.10) U | 6 Weeks | FPG, Insulin dose, Body weight, Nocturnal hydroglycemic events, Hypoglycaemic events, Adverse events |
| Hassanein M | Algeria, India, Lebanon, | Adults (y ≥ 18 for In- | 131 | 132 | (42.60-63.50) | (38.40-61.70) U | 32 Weeks | FPG, Insulin dose, HbA1c, Nocturnal |

**Table 1:** Continued…

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| et al. 2018 (14) | Malaysia and South Africa | dia, Lebanon, Malaysia and South Africa, and y ≥ 19 for Algeria) with type 2 diabetes | | | U | | | hydroglycemic events, Hypoglycaemic events, Adverse events |
| Yang W et al. 2019 (15) | China | Adults (y ≥ 18) with type 2 diabetes | 361 | 182 | (9.57-27.15) U | (9.87-27.17) U | 26 Weeks | FPG, Insulin dose, Body weight, HbA1c, Nocturnal hydroglycemic events, Hypoglycaemic events, Adverse events |
| Itoh M et al. 2021 (16) | Japan | Patients (y < 75) with type 2 diabetes | 13 | 9 | (2.80-24.00) U | (10.40-25.6) U | 52 Weeks | FPG, Body weight, HbA1c |

Note. RCTs: Randomized Controlled Trials; IDegAsp: insulin degludec/insulin aspart; BIAsp 30: biphasic insulin aspart 30; NA: Not Applicable; FPG: fasting plasma glucose; HbA1c: Glycosylated hemoglobin

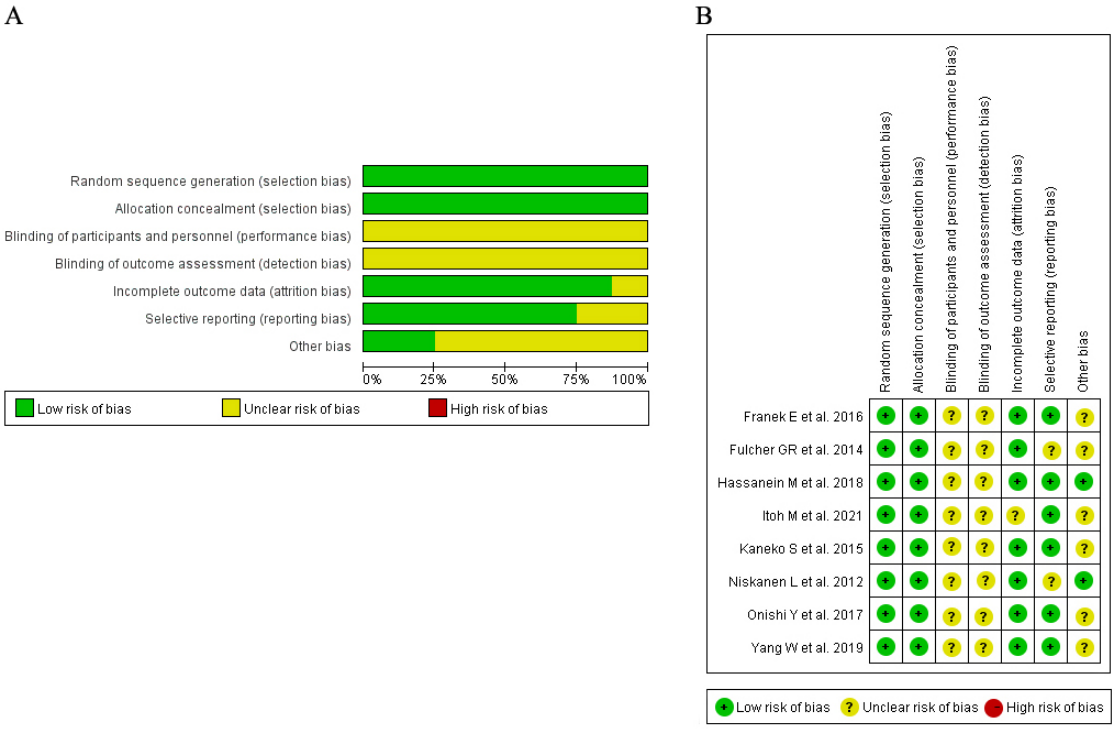


**Fig. 2: Risk bias evaluation of included RCTs.** (A) Evaluation of overall risk bias in RCTs; (B) Bias risk assessment for each RCT

### *Meta-analysis results of RCTs*

IDegAsp was significantly better to BIAsp30 in improving FPG levels (Fig. 3, MD=-1.30, 95%CI: -1.50 ~ -1.11, *P*<0.001) (9-16) and reducing the endpoint daily average insulin dose (Fig. 4, MD= -0.10, 95%CI: -0.18 ~ -0.03, *P*=0.009; MD= -4.86, 95%CI: -8.65 ~ -1.08, *P*=0.01) (9-15). However, there was no statistically signifi-

cant difference in the improvement of body weight change (MD= -0.00, 95%CI: -0.42~0.42, *P*=0.99) (9-13, 15, 16) and HbA1c (MD = -0.03, 95%CI: -0.11 ~ 0.05, *P*=0.50) (9-12, 14-16) between the two groups. Moreover, IDegAsp significantly reduced the risk of nocturnal hypoglycemic events (Fig. 5, RR = 0.61, 95%CI: 0.52 ~ 0.71, *P*<0.001) (9-15), but there was no statistically significant difference in overall risk of hypoglycemic events (RR=0.97, 95%CI: 0.88 ~ 1.07, *P*=0.57) (9-15) and adverse events (RR=1.01, 95%CI: 0.93~1.09, *P*=0.89) (9-15).

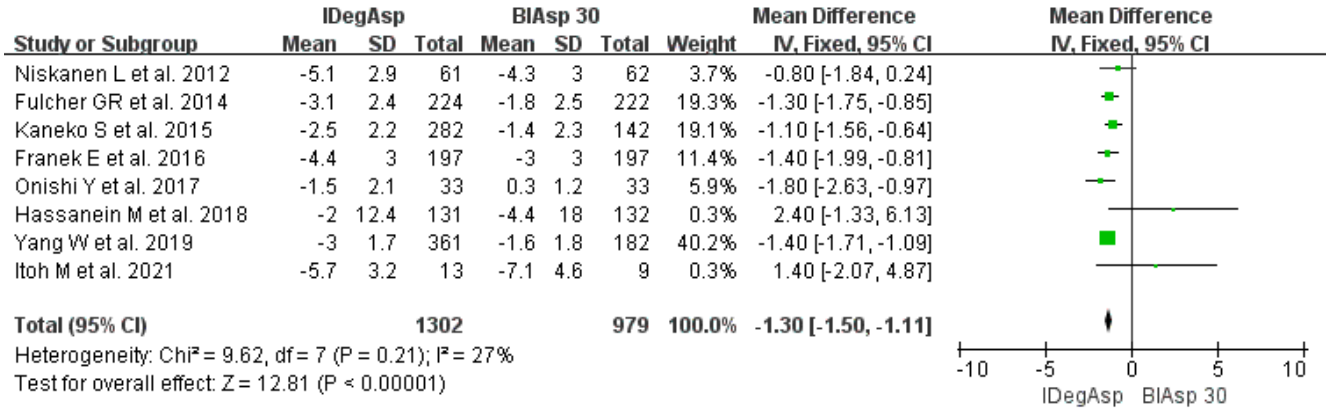


**Fig. 3: Comparison of the effects of IDegAsp and BIAsp 30 on fasting plasma glucose.** df = degrees of freedom

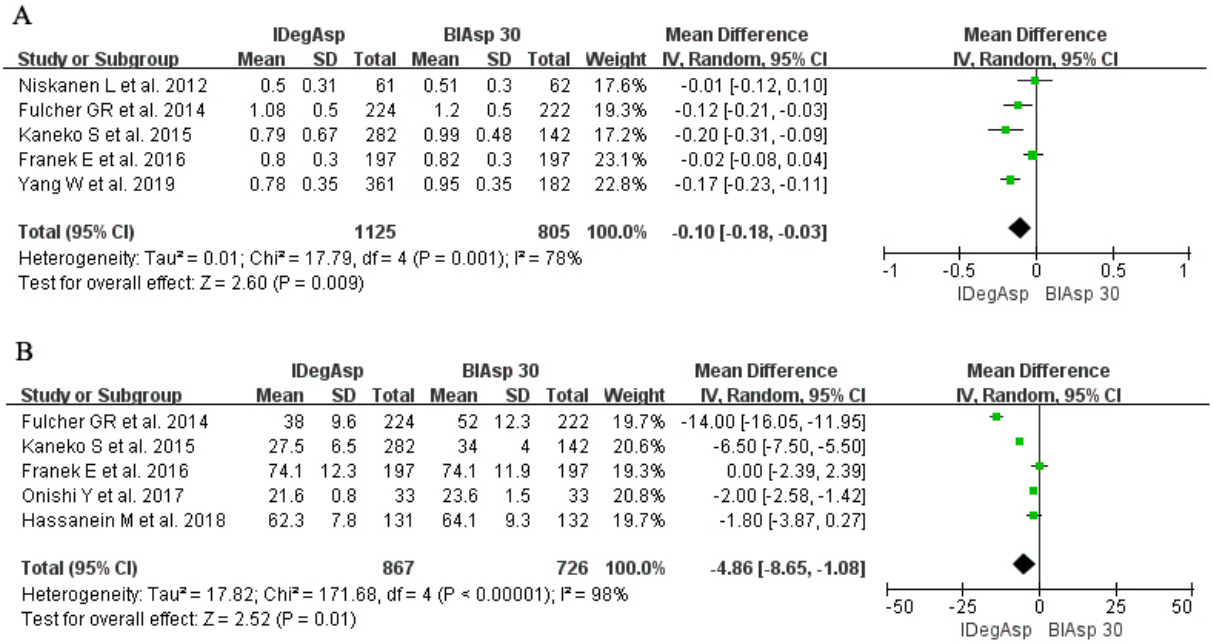


**Fig. 4: The effect of IDegAsp and BIAsp30 on endpoint daily insulin usage.** (A) Insulin usage dosage: U/kg; (B) Insulin usage dosage: U/daily. df = degrees of freedom

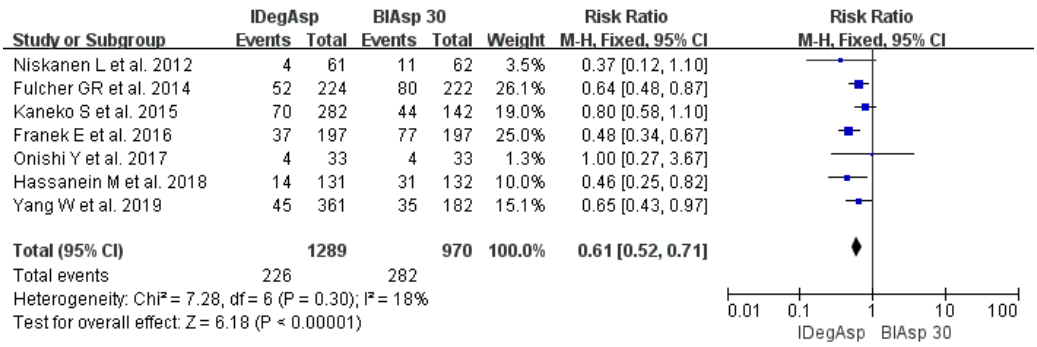


**Fig. 5: The effect of IDegAsp and BIAsp30 on nocturnal hydroglycemic events.** df = degrees of freedom

### *Evaluation of publication bias*

We used Begg's and Egger's tests to evaluate the degree of publication bias in RCTs. Our results showed *P*>0.05 in Begg's and Egger's tests for all RCTs, suggesting no publication bias exsit in all included literature (Fig. 6).

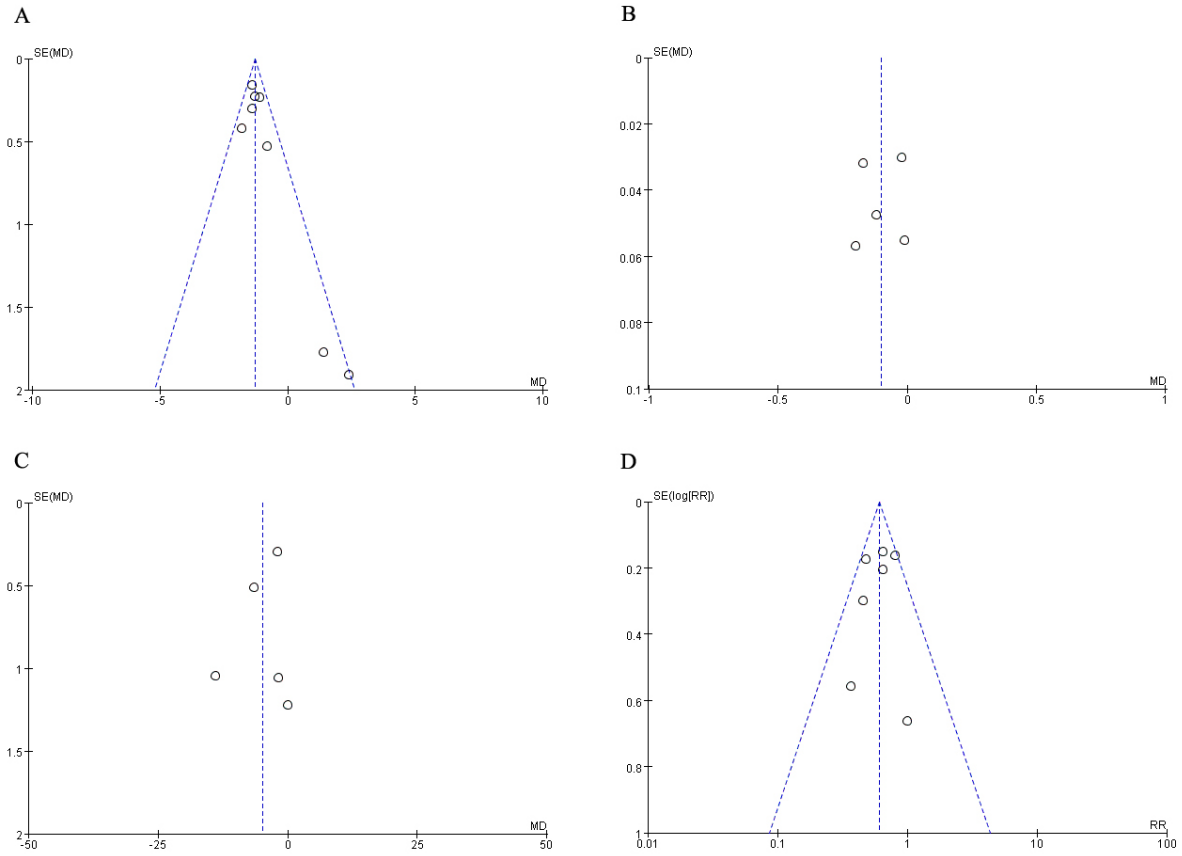


**Fig. 6: Evaluation of publication bias for included RCTs.** (A) Fasting plasma glucose (Begg's test, *P*=0.213; Egger's test, *P*=0.362); (B) Endpoint daily insulin usage (Insulin usage: U/kg) (Begg's test, *P*=0.375; Egger's test, *P*=0.153); (C) Endpoint daily insulin usage (Insulin usage: U) (Begg's test, *P*=0.469; Egger's test, *P*=0.188); (D) Nocturnal hydroglycemic events (Begg's test, *P*=0.621; Egger's test, *P*=0.185). SE: standard error; MD: mean difference; RR=risk ratio

## Discussion

Our meta-analysis included 8 high-quality RCTs to evaluate the efficacy and safety indicators of IDegAsp versus BIAsp30. Our analysis results indicated that compared with BIAsp30, IDegAsp could significantly reduce FPG levels, insulin dosage, and the risk of nocturnal hypoglycemic events in T2D patients, without increasing the overall risk of adverse events. IDegAsp has significant efficacy and safety for T2D patients.

T2D is a progressive metabolic disease, with an incidence of 11.6% among Chinese residents (17). At present, T2D patients mainly exhibit clinical features such as abnormal insulin secretion, and as the disease progresses, pancreatic islets β Further decline in cell function increases the difficulty of blood sugar control (18). Actively controlling blood glucose can significantly delay the progression of complications related to T2D, among which oral hypoglycemic drugs are the preferred method for treating T2D (19). For T2D patients with poor oral medication treatment, insulin is a commonly used choice. Although there are various types of drugs, the blood glucose compliance rate is relatively low.

IDegAsp is a new type of premixed insulin, made by mixing long-acting insulin and quick acting insulin in a fixed ratio (70% IDeg and 30% IAsp) and dissolving them in a certain concentration of zinc and phenol (20). IDeg is a dimer, while IAsp is a monomer, each of which exists in a stable and soluble form (21). Compared to other pre mixed insulin injections, IDegAsp does not need to be paused before injection. IDegAsp can effectively simulate insulin secretion in the body; regulate FPG and postprandial blood sugar. Studies showed that IDegAsp could be an optimal treatment option for T2D patients with poor blood sugar control (22-24). Our meta-analysis found that compared to BIAsp30, IDegAsp could better control FPG and significantly reduce the endpoint daily insulin dosage, while having no significant impact on body weight and HbA1c. Our results indicated that IDegAsp had significant efficacy and safety in T2D patients.

The fluctuation of blood glucose, especially the occurrence of postprandial hyperglycemia, can promote the occurrence of oxidative stress injury and increase the risk of atherosclerosis (25, 26). Hypoglycemia is a common adverse reaction during insulin therapy, which can increase the risk of various adverse outcomes such as vascular events and cognitive dysfunction (27, 28). The occurrence of nocturnal hypoglycemia can often lead to neurological and cardiovascular damage due to untimely intervention, and in severe cases, it can lead to death (29). Our analysis found that compared with BIAsp30, IDegAsp significantly reduced the risk of nocturnal hypoglycemic events, without increasing the overall risk of adverse events. It indicates that IDegAsp is safer than BIAsp30 for T2D patients.

Our meta-analysis has the following limitations. Firstly, although the quality of the literature on the 8 RCTs we included is high, the overall sample size is small, which may have a potential impact on the research results. Secondly, due to possible differences in data acquisition, this may lead to some heterogeneity in the results. Thirdly, some of the included studies being open-label and not using blind methods, so this may lead to reporting bias. Fourthly, due to the number of literatures, we did not conduct subgroup analysis of the results.

## Conclusion

Compared with BIAsp30, IDegAsp could significantly reduce FPG levels, insulin dosage, and the risk of nocturnal hypoglycemic events in T2D patients, without increasing the overall risk of adverse events. IDegAsp has good hypoglycemic efficacy and safety, and has broad clinical application prospects. IDegAsp will bring new options for personalized treatment by clinician, benefiting more T2D patients.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

## Acknowledgements

Not Applicable.

## Conflict of Interest

No conflicts of interest to declare.

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