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Review Article

Effectiveness of Faster Aspart versus Insulin Aspart in Children with Type 1 Diabetes: A Meta-Analysis

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Abstract

Background: Intensive insulin regimens are recommended to achieve glycemic goals in children and adolescents with type 1 diabetes. Fast-acting insulin aspart (faster aspart) is a new formulation of insulin aspart (IAsp) in which L-arginine and niacinamide are added to assure formulation stability, early absorption, and ultra-fast action. This meta-analysis compares faster aspart with IAsp for blood sugar control in children with type 1 diabetes. This study suggested treating diabetes with insulin, especially in children with type 1 diabetes.

Methods: PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, and Google Scholar were searched from 2000 to 2023 without language restrictions. Blood glucose monitoring, HbA1c, care model, insulin aspart, IAsp, faster aspart, type 1 diabetes, and pediatrics are Mesh keywords. Cochrane Q statistics and index tested heterogeneity. To account for heterogeneity, Q=145.99 (*P*-value < 0.001) and =97.26%, and the random-effect model was used to aggregate primary study results. The meta-analysis of randomized-controlled trials was conducted in accordance with PRISMA standards.

Results: The overall estimate measure i.e. mean difference was found to be 5.44 [0.45, 10.44] and 7.71 [7.16, 8.26] which indicate significant reduction in the HbA1C level in the fast acting insulin aspart group as compared to the IAsp in T1D. However, the mean difference with respect to BMI was found to be -0.06 [-0.60, 0.48] which indicate non-significant reduction.

Conclusion: Faster aspart had faster onset and more early exposure than IAsp in children and adolescents with greater and more variable anti-insulin antibody levels than adults did. Hence fast-acting insulin aspart may provide better glucose control than IAsp in T1D.

Keywords: Insulin aspart; IAsp; Faster aspart; Diabetes type 1; Care model

Introduction

Type 1 diabetes is a multifactorial immune-mediated disease that results from a genetic predisposition that leads to the autoimmune destruction of insulin-producing β cells in pancreatic islets. Alarmingly, type 1 diabetes is increasing world-

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wide, especially in young children (1-6). It is predicted that number of diabetic people will rise to 643 million by 2030 and 783 million 2045 (7). The management of type 1 diabetes is a complex process. Patients with diabetes have demands that extend beyond just maintaining good glucose control and include preventing complications, limiting their impairment, and receiving rehabilitation. In several studies, organizational leaders in healthcare systems initiated system-wide reorganizations to facilitate more comprehensive and coordinated diabetes care. In the effective control of diabetes, daily tasks include frequent monitoring of blood sugar, carbohydrate counting, calculating and preventing hyperglycemia and hypoglycemia, and prescribing insulin doses (8-9).

The pharmacokinetics of exogenous insulin in children and adolescents with type 1 diabetes (T1D) has been determined by measuring free insulin or total insulin (10). Rapid-acting insulin aspart (faster aspart) is a new formulation of insulin aspart (IAsp) in which two additional excipients, L-Arginine and Niacinamide, are included to ensure formulation stability with early absorption and ultra-fast action. This translates to an earlier onset of action, a 74% greater initial 30-minute glucose-lowering effect, and a reduction in postprandial glucose (PPG) levels for faster aspart (11-12). In children and adolescents, based on free IAsp, faster aspart also has accelerated pharmacokinetics and has shown PPG-lowering potential relative to IAsp. In several phase 3 trials comparing faster aspart and IAsp, including one in children and adolescents, faster aspart provided better PPG control, overall glycemic control at least as reasonable as IAsp, and a similar or reduced overall risk of hypoglycemia (13). The efficacy of aspartate in patients with diabetes, including children and adolescents, has been assessed to be limited. Therefore, faster aspart may be able to fulfill the unmet need not only in adults but also in children and adolescents with diabetes for ultrafast mealtime insulin with absorption characteristics that had better resemble endogenous insulin secretion in healthy subjects.

We aimed to examine and analyzes the results of studies comparing the effects of faster aspart and IAsp in children with type 1 diabetes.

Methods

The meta-analysis of randomized-controlled trials was conducted in accordance with PRISMA standards.

Search strategy

The databases were searched from PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, and Google scholar from 2000 to 2023 with no language limitation. The reference lists of recent strategies and qualified articles were reviewed. The keywords and Mesh terms used are Blood glucose monitoring AND HbA1c AND insulin aspart OR IAsp AND faster aspart AND type 1 diabetes pediatrics. To confirm that we included all eligible trials, we accompanied a last search before submission. Finally, we communicated with authors of published abstracts to provide their trial data if not yet published.

Study selection

Papers of relevant studies were assessed in duplicate and individually for inclusion and exclusion criteria by two reviewers (JW and YW). Data extraction included author (year), country, type of study, total patients, sex, BMI, HbA_{1c}, and concentration for parallel RCTs. The standard data extraction and any disagreement were resolved by conversation.

The inclusion and exclusion criteria

The inclusion criteria was all of articles that compare faster aspart versus IAsp in children, case control study, cohort study, and clinical trial study. The exclusion criteria in this study was all of articles that compare faster aspart versus IAsp in adolescents and adults, review article, case report study, case series study, systematic review study, and letter to the editor study.

Quality assessment

Two authors (JW and YW) individually evaluated the included articles for quality assessment, and the screening process and inclusion/exclusion criteria were assessed according to the PRISMA checklist (Fig. 1).

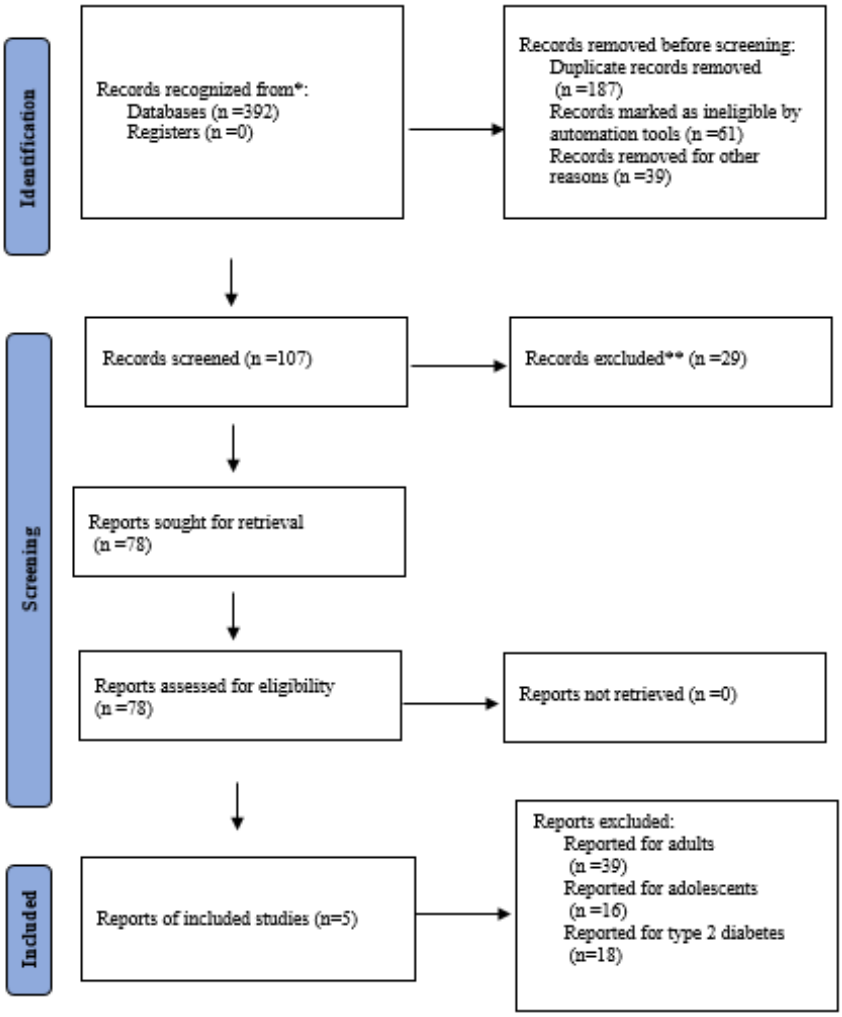

Fig. 1: Flowchart of the selection of studies

Certainty assessment

The corresponding 95% confidence intervals (CIs) were considered for dichotomous outcomes by applying fixed-effects or random-effects models according to heterogeneity.

Reporting bias assessment

The visual inspection of the Funnel plot and Egger's regression asymmetry and Begg's test were applied to evaluate potential publication bias among included studies in the meta-analysis.

Statistical analysis

The STATA software was used for data analysis. Mean differences were considered as the effect size for comparing the two groups. The needed information for review articles was summary statistics (mean, standard deviation and sample size in each group). Cochrane's Q statistics performed the heterogeneity test (a low P-value provides evidence of heterogeneity) and the $I^{\wedge 2}$ index (unimportant heterogeneity was indicated as $I^{\wedge 2} < 40\%$ and considerable heterogeneity were shown as $I^{\wedge 2}$

> 75%). A random-effect meta-analysis was used to incorporate the results when heterogeneity exists; the otherwise fixed-effect model was used. Publication bias was assessed by funnel plot and regression-based egger test.

Results

Compare the Body Mass Index (BMI) of two groups Insulin aspart (IAsp) and Faster aspart

Fig. 2 shows the incorporating result of four primary studies to compare the BMI of two groups (IAsp and Faster aspart). Since Q=0.03 (*P*-value =1.00) and I^2=0.0%, primary studies are homogenous, and a fixed-effect model was used. The pooled estimate of the mean difference of BMI equals -0.6 with a 95% confidence interval (-0.60, 0.48) which indicate non-significant differences between the two groups regarding BMI. The funnel plot and Egger test (P-value=0.863) indicated no publication bias (Fig. 3).

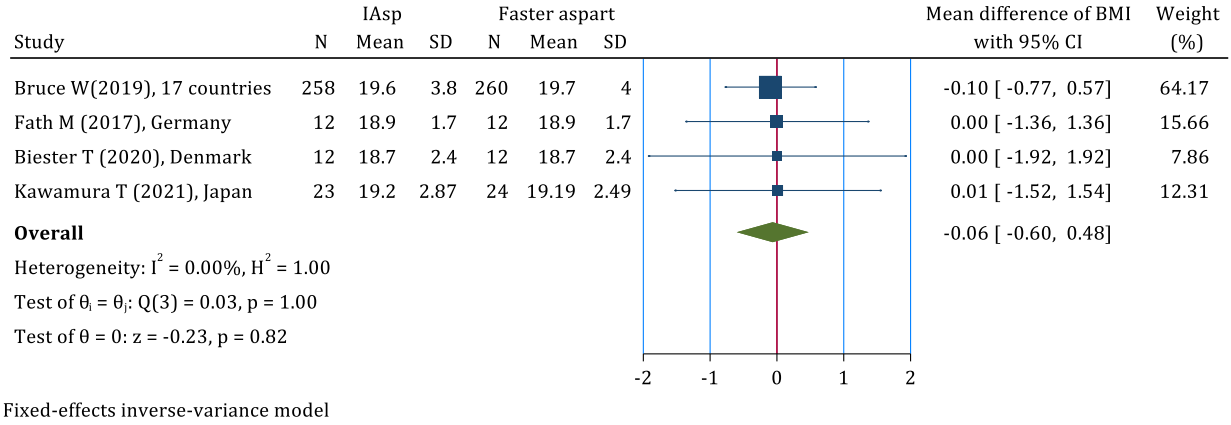

Fig. 2: Forest plot of mean dereference of BMI between IAsp and Faster aspart groups

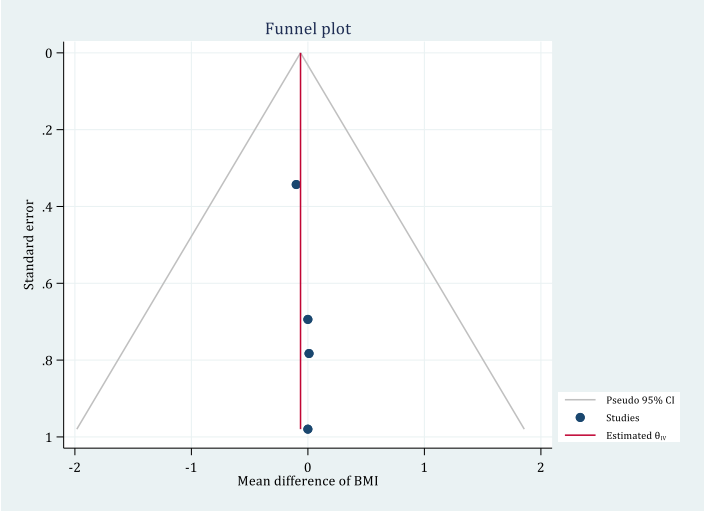

Fig. 3: Funnel plot of mean difference of BMI to investigate the publication bias

Comparison of Glycated hemoglobin (HbA1c) in two groups of IAsp and aspart faster

Figure 4 shows the incorporating result of five primary studies to compare the HbA_{1c} (mmol/mol) of two groups (IAsp and faster aspart). The pooled

estimation is 5.44 with a 95% confidence interval (0.45, 10.44). To consider the heterogeneity, Q=145.99 (*P*-value < 0.001) and I^2=97.26%, and Random-effect model was used to combine the result of primary studies. To test the overall estimation, the *P*-value = 0.03, so the mean of HbA_{1C} (mmol/mol) in IAsp group was significantly higher than the faster aspart group. The funnel plot and Egger test (*P*-value=0.931) indicated no significant involvement of publication bias (Fig. 5).

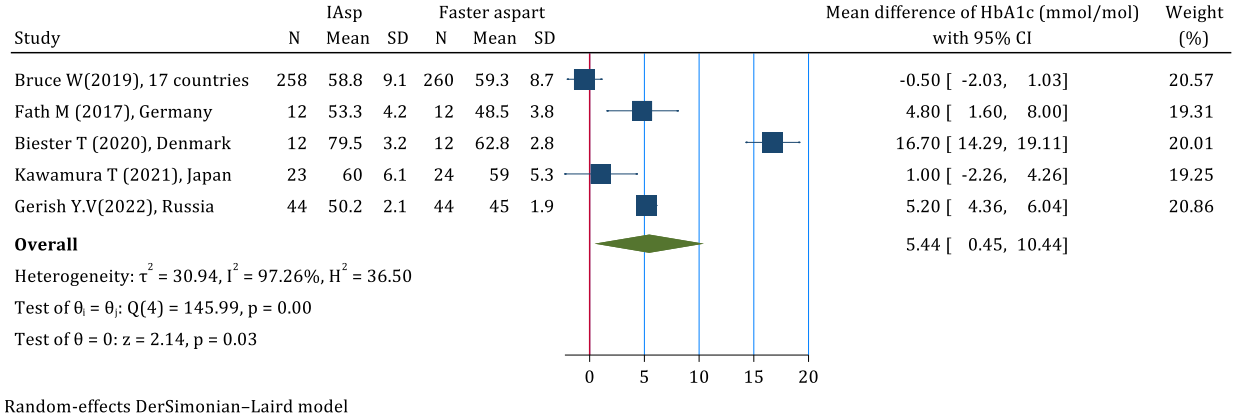

Fig. 4: Forest plot of mean dereference of HbA_{1C} (mmol/mol) between IAsp and Faster aspart groups

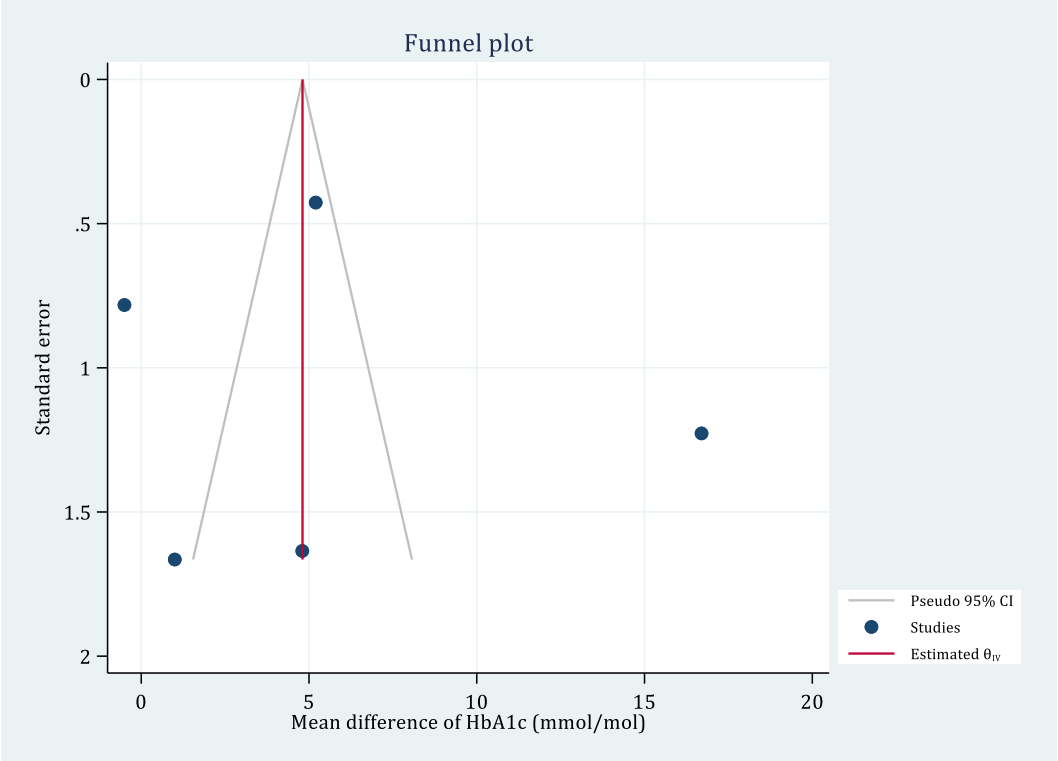

Fig. 5: Funnel plot of mean difference of HbA_{1C} (mmol/mol) to investigate the publication bias

To combine the result of primary studies in Baseline HbA_{1C} and Baseline HbA_{1C} (mmol/mol), the Mean was considered as the effect size, and the needed information of review articles were summary statistics (mean, standard deviation, and sample size). The pooled mean estimation for Baseline HbA_{1C} was 7.71 with a 95% confidence interval (7.16, 8.26). The heterogeneity indexes, Q=1.43 (*P*-value = 0.084) and I^2=0.00% led us to use the fixed-effect model to combine the results of primary studies. (Fig. 6). The funnel plot and Egger test (*P*- value=0.329) indicated no publication bias (Fig. 7).

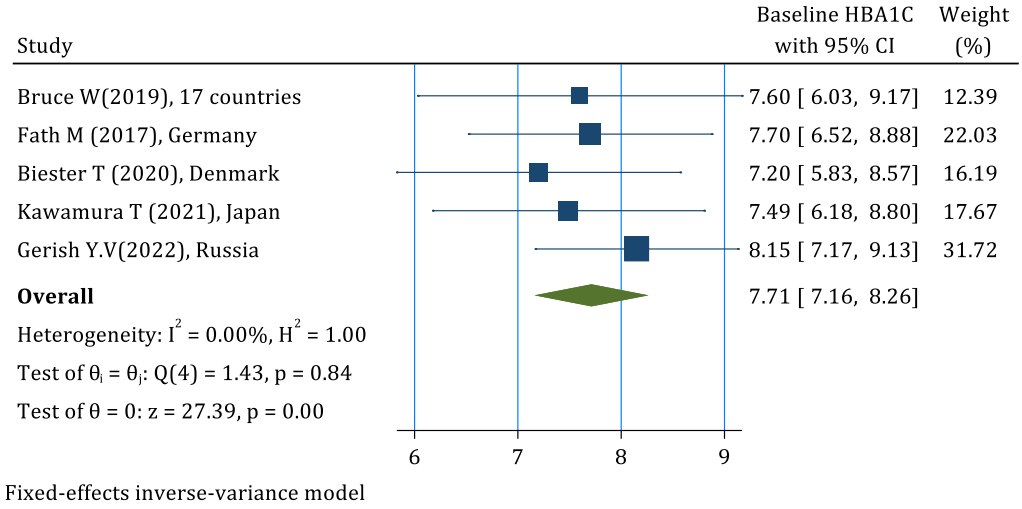

Fig. 6: Forest plot of Baseline HbA_{1C} mean

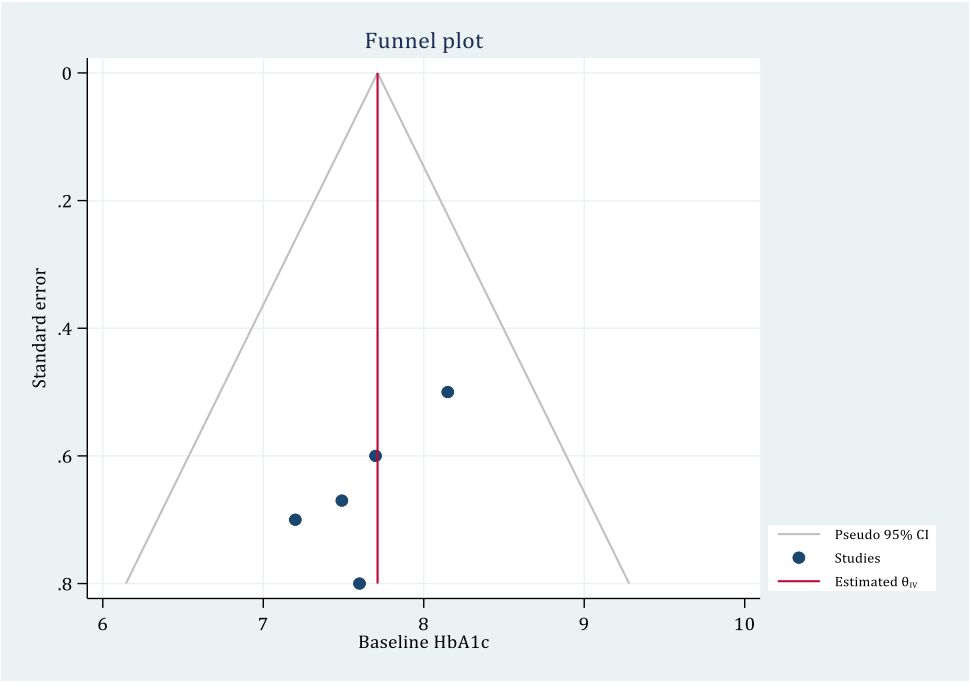

Fig. 7: Funnel plot of Baseline HbA_{1C} means to investigate the publication bias

The pooled mean estimation for the mmol/mol baseline is 58.70 with a 95% confidence interval (50.97, 66.44). The heterogeneity indexes, Q=0.26 (*P*-value = 0.97) and I^2=0.00%, also led us to use the fixed-effect model to combine the result of primary studies (Fig. 8). The funnel plot and Egger test (*P*-value=0.772) indicated no publication bias (Fig. 9).

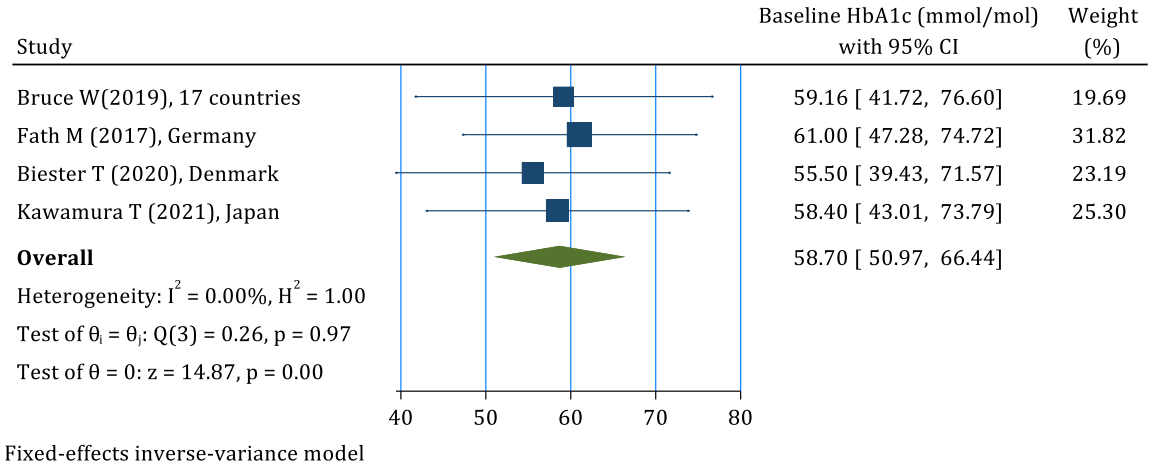

Fig. 8: Forest plot of Baseline HbA_{1C} (mmol/mol) baseline mean

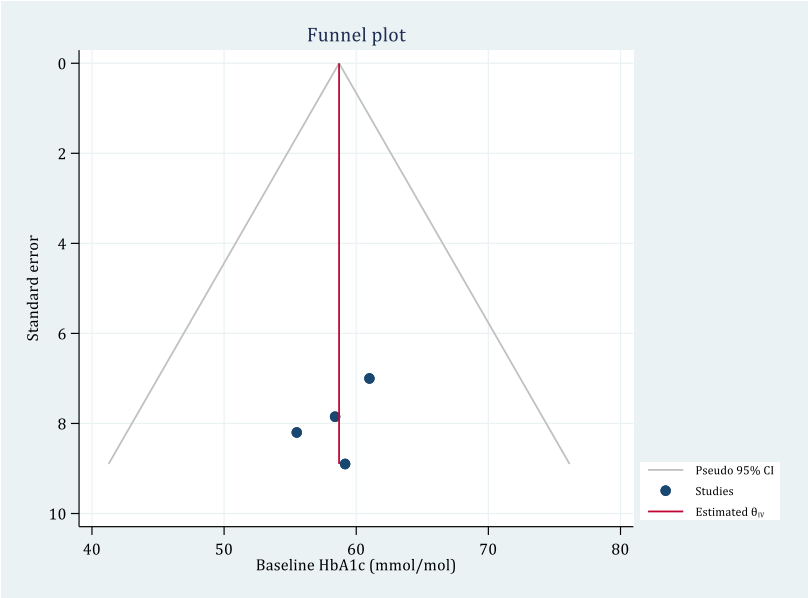

Fig. 9: Funnel plot of Baseline HbA_{1C} (mmol/mol) means to investigate the publication bias

Certainty of evidence

Considering that the articles included in this meta-analysis were published in reliable journals and the results of each study were checked separately in terms of certainty in the results in terms of bias, the articles in the meta-analysis have been examined. We could definitely refer to the results of this meta-analysis.

Discussion

Recent substantial research efforts have been dedicated to investigating the comparative effects of "faster aspart" versus "insulin aspart" on various parameters in pediatric patients with type 1 diabetes (T1D) (11-13). These investigations encompass changes in body weight and levels of glycosylated hemoglobin. Furthermore, delving into the potential advantages of utilizing a combination insulin regimen, which includes a long-acting basal insulin analog in conjunction with a rapid-acting insulin analog, may offer a promising approach to address the individualized requirements of children with T1D and optimize glycemic management. However, exact effect is unclear so far. Meta-analysis is one of the quantitative approaches, which provide overall estimate of studies, and helps to provide evidence for better clinical decision (14-16).

The present meta-analysis compared faster aspart and IAsp in children and adolescents for better control of blood sugar. The fundamental characteristics of the studies included in the meta-analysis has been summarized in Table 1.

Table 1: The fundamental characteristics of the studies included in the meta-analysis

Reference Number	*Type of study*	*Total patients*	*Iasp patients*	*Faster aspart patients*	*BMI (Iasp) mean*	*BMI (Faster aspart) mean*	*Hba1c baseline (%) mean*	*mmol/mol baseline (mean)*
25	NCT02670915	518	258	260	19.6	19.7	7.6	59.16
18	NCT02035371	12	12	12	18.9	18.9	7.7	61
27	NCT03407599	12	12	12	18.7	18.7	7.2	55.5
26	NCT0267091	47	23	24	19.2	19.19	7.49	58.4
28	None	44	44	44			8.15	

A combination of five primary studies was done to compare the amount of HbA_{1c} (mmol/mol) in two groups, IAsp and faster apart. For the general estimation test, *P*-value = 0.03, the statistical analysis showed that the average HbA_{1c} (mmol/mol) in the faster aspart group is significantly lower than the IAsp group. The total insulin (i.e., bound and unbound insulin) can be measured without prior steps; the size of the free and unbound fraction requires that anti-insulin antibodies be precipitated using polyethylene glycol (PEG) before analysis (17-22).

Pharmacokinetics of exogenous insulin in children and adolescents with type 1 diabetes (T1D) were determined by measuring free insulin10 or total insulin (23-25). Rapid-acting insulin aspart (faster aspart) is a new formulation of insulin aspart (IAsp) in which two additional excipients, L-arginine and niacinamide, are included to ensure formulation stability with early absorption and ultra-fast action. This translates to an earlier onset of action, a 74% greater initial 30-minute glucose-lowering effect, and a reduction in postprandial glucose (PPG) levels for faster aspart (26). In several phase 3 trials comparing faster aspart and IAsp, including one in children and adolescents, faster aspart provided better PPG control, overall glycemic control at least as reasonable as IAsp, and a similar or reduced overall risk of hypoglycemia.

The faster aspart may meet the unmet need in adults, children, and adolescents with diabetes for ultrafast mealtime insulin with absorption characteristics that had better resemble endogenous insulin secretion in healthy persons. The International Society of Pediatric and Adolescent Diabetes (ISPAD) recommends that glycemic control in children with T1D be measured every three months, with a target hemoglobin A1c of less than 7.0% for children, adolescents and young adults who have access to comprehensive care (27).

There are several challenges to achieving reasonable glycemic control without significant hypoglycemia with insulin therapy in children and adoles-

cents with T1D (28). The reasons for this are multifactorial and include avoiding or correcting excessive hypoglycemia, good physical therapy for insulin resistance, increased weight, height, and caloric needs, and unpredictable dietary intake and eating patterns. Clinicians may note that the glycemic response, total daily insulin dose, and rate of severe or BG-confirmed hypoglycemia induced by basal-bolus faster aspart therapy may be influenced by the patient's baseline BMI and HbA_{1c} to not clinically taken a relevant degree. However, in clinical practice, these baseline characteristics, in the context of a broader patient profile, including social and psychological factors, may be used by clinicians to guide clinical decision-making in a patient-centered model of diabetes management. Investigating the association between baseline characteristics (HbA_{1c} and Body Mass Index) and clinical outcomes of Fast-Acting Insulin Aspart in people with diabetes: A post hoc analysis Keith Bowering investigations (29) and statistical analysis of our study showed no difference between IAsp and faster apart groups in terms of BMI (Fig. 2).

Several clinical efficacy studies have been conducted comparing the effect of IAsp and faster apart groups (18, 27-28). In Japanese patients with T1D, the onset of faster aspart was twice faster than IAsp (3.0 vs. 7.1 minutes, respectively; and the early glucose-lowering effect was more significant (18). These results confirm that the pharmacology of faster aspart in Japanese patients is similar to that in European children, adolescents, and adults (28). The onset of 7 trials showed that mealtime faster aspart is lower than IAsp in a change in less hemoglobin A1c 26 weeks after randomization in children and adolescents with T1D. Furthermore, faster aspart is superior to IAsp at mealtime, and faster aspart postmeal time is noninferior to IAsp. This post-hoc analysis aimed to analyze the seven subgroups to evaluate the efficacy and safety of faster aspart versus IAsp, in combination with degludec basal insulin in Japan's children and adolescents with T1D. Experiences of faster aspart in the Japanese population, especially in terms of safety outcomes, for Japanese pediatricians responsible for patients with T1D is valuable. The faster aspart may meet the unmet need in adults, children, and adolescents with diabetes for ultrafast mealtime insulin with absorption characteristics that had better resemble endogenous insulin secretion in healthy persons. The International Society of Pediatric and Adolescent Diabetes (ISPAD) recommends that glycemic control in children with T1D be measured every three months, with a target hemoglobin A1c of less than 7.0% for children, adolescents, and young adults who have access to comprehensive care (19).

There are several challenges to achieving reasonable glycemic control without significant hypoglycemia with insulin therapy in children and adolescents with T1D. The reasons for this are multifactorial and include avoiding or correcting excessive hypoglycemia, good physical therapy for insulin resistance, increased weight, height, and caloric needs, and unpredictable dietary intake and eating patterns. In a study by Biester et al (27) point estimates for comparing faster aspart versus IAsp favored faster aspart. Furthermore, the vast majority of differences were statistically significant despite the relatively small number of subjects. It was observed that, among children, adolescents, and adults with T1D, faster aspart was associated with earlier onset and greater initial exposure than IAsp independent of free or total IAsp measurements. The concentration of total serum IAsp was generally higher than the concentration of free serum IAsp.

In a study by Kawamur et al (26), an analysis of participants from Japan showed that faster aspart meal times might improve blood glucose control compared with IAsp. Importantly, these improvements were observed with faster aspart mealtime with a safety profile comparable to that of IAsp. In their study, the faster onset and greater early exposure for faster-acting aspart versus IAsp in children and adolescents were consistent with adults. It is suggested that ultra-rapid insulin, faster-acting insulin aspart, may provide better mealtime glucose control than present rapid-acting insulins, also in children with T1DM. Bruce W. Bode et al., during a study at the start of 7 trials, showed a sig-

nificant improvement in HbA_{1c} change from baseline with mealtime faster aspart versus IAsp mealtime and HbA_{1c} control with postprandial faster aspart administration compared to mealtime IAsp in children and adolescents whom who have type 1 diabetes. Furthermore, postprandial hyperglycemia was significantly reduced more rapidly with faster aspart versus IAsp, and the overall hypoglycemic profile and safety profile were comparable across treatments (25). Gerish et al. in Russia confirmed the results of previous studies with a study in 2022 (28). The statistical analysis of 5 studies included in the meta-analysis confirmed the results obtained from the studies and showed that faster aspart could significantly improve blood sugar control compared to IAsp, which is mainly in children and adolescents.

One of the study's limitations is the combination of meals that were not determined during the trials. It is assumed that patients received general dietary recommendations from their physicians, so the present study better reflects real-world clinical practice. Another limitation of the analysis is the small sample size; however, the findings presented from the statistical analysis are done according to the limitations, but the results can be precious for clinical professionals.

Conclusion

Continued improvement in long-term glycemic control, hypoglycemic risk management, and dose flexibility are essential with intensified insulin therapy in children and adolescents. Intensive insulin regimens are recommended to achieve glycemic goals in children and adolescents with type 1 diabetes, which leads to better glycemic control and reduced risk of chronic complications. In conclusion, the current findings of the present meta-analysis are faster onset and more early exposure for faster aspart versus IAsp in children and adolescents consistent with adults and suggest faster-acting insulin aspart may provide better glucose control than IAsp in T1D.

Journalism Ethical 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

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Conflict of Interest

The authors declare that there is no conflict of interests.

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