Clinical efficacy and safety of insulin aspart compared with regular human insulin in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis

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INTRODUCTION
Prandial insulin is a key component in insulin treatment of type 1 diabetes mellitus (T1DM) and in many patients with type 2 diabetes mellitus (T2DM). The evidence-based data supporting the choice of an insulin preparation are still limited.

OBJECTIVES
We performed a systematic review to summarize and update the evidence on relative efficacy and safety of insulin aspart (IASp) and regular human insulin (RHI) in both types of diabetes.

METHODS
Randomized controlled trials comparing IASp with RHI in patients with either T1DM or T2DM and conducted until May 2013 were retrieved from a systematic search of MEDLINE, EMBASE, and Cochrane Library.

RESULTS
Of 16 relevant trials, 11 involved patients with T1DM and 5—with T2DM. In the T1DM population, IASp, when compared with RHI, provided a greater reduction in hemoglobin A₁c (HbA₁c) levels (weighted mean difference [WMD], –0.11%; 95% confidence interval [CI], –0.16 to –0.05; WMD, –1.2 mmol/mol; 95% CI, –1.7 to –0.5), and improved postprandial glucose levels following breakfast (WMD, –1.40 mmol/l; 95% CI, –1.72 to –1.07), lunch (WMD, –1.01 mmol/l; 95% CI, –1.61 to –0.41), and dinner (WMD, –0.89 mmol/l; 95% CI, –1.19 to –0.59). The risk of nocturnal hypoglycemia was lower in T1DM patients receiving IASp (relative risk, 0.76; 95% CI, 0.64–0.91), while no difference was observed for severe hypoglycemia. In T2DM patients, IASp led to a greater reduction in HbA₁c levels (WMD, –0.22%; 95% CI, –0.39 to –0.05; –2.4 mmol/mol, –4.3 to –0.5) and postprandial blood glucose. The risk of overall hypoglycemia and severe adverse effects was comparable between the groups.

CONCLUSIONS
IASp provides better glycemic control when compared with RHI in patients with T1DM and T2DM. Fewer T1DM patients treated with IASp experienced nocturnal hypoglycemia, while both interventions showed a comparable risk of severe hypoglycemic events in both types of diabetes.

INTRODUCTION
The clinical practice guidelines recommend the use of insulin preparations in all patients with type 1 diabetes mellitus (T1DM) and in subjects with type 2 diabetes mellitus (T2DM) with uncontrolled glycemia despite the use of combined therapy including several oral antidiabetic drugs (OADs) or a glucagon-like peptide 1 (GLP-1) agonist.¹⁻⁴ Insulin therapy is also recommended as a first-line treatment in T2DM subjects with highly uncontrolled hyperglycemia.¹ In patients with T1DM, in whom insulin secretion is completely abolished because of β-cell destruction, the current guidelines recommend intensive insulin therapy mimicking physiological insulin
profile. This can be achieved with either multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) using insulin pumps. Unlike in T1DM, most T2DM patients retain some endogenous insulin secretion, although the disease is characterized by progressive \( \beta \)-cell insufficiency. Therefore, treatment of T2DM should be individualized based on the degree of insulin deficiency and some clinical factors. In T2DM, intensive insulin therapy is usually used in relatively young and active subjects in whom OADs, GLP-1 agonists, or simple regimens of insulin therapy are ineffective. Long-term studies demonstrated that intensive hypoglycemic therapy is effective in lowering hemoglobin A\(_1c\) (HbA\(_1c\)) levels and reducing the risk of microvascular complications in patients with both T1DM and T2DM. As the number of relatively young TD2M patients with long life expectancy is growing, intensive insulin therapy is becoming increasingly common in this type of diabetes. However, intensive blood glucose control predisposes to severe hypoglycemia and increased body weight when compared with conventional therapies. Severe hypoglycemia is associated with many unfavorable clinical outcomes; therefore, the choice of an optimal diabetes treatment should include a consideration of its potential to control glycaemia as well as associated risk of hypoglycemia.

Available insulin preparations show different pharmacological properties with respect to the time of onset, peak activity, and duration of action. Regular human insulin (RHI) has been an integral component of intensive insulin treatment for several decades. RHI provides effective mealtime coverage; however, it also presents several limitations related to its pharmacological profile. RHI is characterized by a delayed time of onset (about half an hour after the injection) with the maximum activity and serum concentration levels after 2 to 3 hours, and prolonged action lasting 6 to 8 hours. Therefore, patients should administer RHI about 30 minutes before meals and consume a snack several hours later to avoid late hypoglycemia. To overcome these limitations, rapid-acting insulin analogs (RAAs) have been designed. Insulin aspart (IASp) is one of the 3 RAAs available on the market, the 2 other being insulin lispro and glulisine. IAsp was developed by a modification of human insulin through a single amino-acid substitution of proline by aspartic acid in the 28th position of the B chain. IAsp is growing, intensive insulin therapy is becoming increasingly common in this type of diabetes.

The relative efficacy and safety of IAsp and RHI in diabetic patients has been a matter of ongoing debate. Some new evidence has been published since we first compared both interventions as a prandial or premixed approach in a systematic review. We hope that the inclusion of new data into our analysis will improve its credibility and allow to conduct an assessment in a much more homogenous group of studies. The aim of the current study was to perform a systematic review to summarize and update the evidence on relative efficacy and safety of IAsp and RHI in both types of diabetes in patients receiving prandial insulin treatment.

**METHODS** Search strategy We carried out a systematic search of major medical databases including Medline (via PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant clinical evidence. The search strategy comprised keywords referring to diabetes mellitus and IAsp, which were combined with appropriate Boolean operators. Finally, the results of the systematic search were limited to records containing keywords relating to randomized controlled trials (RCTs). Databases were searched until May 2013. We also screened registers of ongoing clinical trials (clinicaltrials.gov, ISRCTN.org), proceedings of meetings organized by the associations active in the field of diabetes (American Diabetes Association, European Association for the Study of Diabetes), and references of identified articles to retrieve potentially relevant information.

Inclusion and exclusion criteria Eligible RCTs should directly compare IAsp with RHI in patients with T1DM or T2DM using prandial insulin therapy with or without basal insulin and provide similar other antidiabetic medications in both treatment arms. Studies with at least 12 weeks of follow-up were included. Studies were excluded from this analysis when patients had pregestational or gestational diabetes, less than 10 patients were recruited for the study, or if the studies were designed to compare different schemes of prandial insulin treatment in each group, that is, MDI vs. CSII. Studies published in languages other than English, French, and German were also not considered in this review.

Study selection and credibility assessment Two independent analysts retrieved articles at each stage of the selection process and assessed credibility of the included trials. Any discrepancies between the analysts were solved by consensus or a third party. Methodological quality was assessed according to the criteria proposed by Jadad et al. Scores from 0 to 5 points were granted depending on the fulfillment of the following criteria: randomization and its method, blinding and correctness of its method, and information concerning patients lost to follow-up. A higher number of granted points reflected higher credibility.
RESULTS Study flow The search in electronic databases resulted in 3504 records, of which 469 were selected for full-text assessment after duplicate removal and abstract analysis. A total number of 453 publications were considered irrelevant and were excluded due to the reasons presented in the publication flow diagram, mainly owing to incorrect interventions, inadequate length of follow-up, and incorrect methodology. Finally, 16 RCTs were considered relevant for the current review (FIGURE 1), including 11 papers referring to T1DM and the remaining 5 involving T2DM patients.

Patients with type 1 diabetes mellitus Study characteristics A total number of 11 RCTs comparing IAsp with RHI in an overall number of 3447 patients with T1DM were retrieved, including 4 studies recruiting children21–24 and 7 trials involving adult patients (FIGURE 1).25–31 The mean duration of diabetes was between 1.8 and 5.2 years and 4.7 and 15.7 years in studies recruiting children and adults, respectively. The mean HbA1c levels at baseline ranged from 7.3% (56 mmol/mol) to 8.6% (70 mmol/mol) in all identified studies. In 10 studies, patients received intensive insulin therapy by MDI using either neutral protamine Hagedorn (NPH) insulin (8 RCTs) or long-acting...


<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Number of patients</th>
<th>Mean age, y</th>
<th>Male sex, % of patients</th>
<th>Mean diabetes duration, y</th>
<th>Mean baseline HbA₁ⱼ, % (mmol/mol)</th>
<th>Mean baseline BMI, kg/m²</th>
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<th>Duration of intervention, wk</th>
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<td>56</td>
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<td>8.1 (65)</td>
<td>MDi/NPH</td>
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<sup>a</sup> values include patients receiving from the third study arm: – insulin lispro (n = 25); <sup>b</sup> median; <sup>c</sup> body weight (kg)

Abbreviations: BMI, body mass index; co, crossover; db, double-blinded; IAsp, insulin aspart; LAA, long-acting insulin analog; MDi, multiple daily insulin; NA, not assessed; NPH, neutral protamine Hagedorn; ol, open-label; pg, parallel-group; RHI, regular human insulin
Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; SD, standard deviation; WMD, weighted mean difference; others, see FIGURE 2

Relative change in hemoglobin A1c levels for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IAsp</th>
<th>RHI</th>
<th>WMD (95% CI)</th>
<th>weight, %</th>
<th>WMD (95% CI)</th>
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<td>n  mean SD</td>
<td>fixed effect model</td>
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<td>Ampudia-Blasco, 2005</td>
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<td>Arslanian, 2005</td>
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<td>14.74 0.03 (–0.11 to 0.17)</td>
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<td>Home, 2000</td>
<td>698 7.88 0.80</td>
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<td>21 7.60 0.70</td>
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<tr>
<td>Tamás, 2001</td>
<td>209 8.02 0.72</td>
<td>210 8.18 0.72</td>
<td>15.20 –0.16 (–0.30 to –0.02)</td>
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</table>

test for heterogeneity: $Q = 6.49, df = 8 (P = 0.5928), P = 0.00%$

test overall effect: $Z = –3.92 (P < 0.0001)$

FIGURE 2 Relative change in hemoglobin A1c levels for comparison between insulin aspart and regular human insulin in patients with type 1 diabetes

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; SD, standard deviation; WMD, weighted mean difference; others, see TABLE

insulin analogues (LAAs) (2 RCTs) as basal insulin. In the remaining RCT, insulin was administered via CSII. 26 Ten studies were carried out according to a parallel design. 21,22,24,27,29-31 Two other RCTs were conducted with a cross-over design 22,25; however, only 1 study provided an adequate wash-out period before the treatment switch. 28 The methodological quality of the included studies ranged from 1 to 3 points, according to the Jadad score, and was most often downgraded because of an open-label design and insufficient information regarding the number of patients lost to follow-up. Allocation concealment was considered adequate in 4 RCTs (TABLE). 26,28,31

Glycemic control Glycated hemoglobin Overall, 9 RCTs assessed the change in HbA1c levels during treatment and presented data pertinent for a meta-analysis. 23,24,26-28 In 3 of those studies, IAsp showed a greater reduction in HbA1c levels at the end of treatment, 29-31 while in the remaining 6 RCTs, the difference between the groups was not significant. Pooled results revealed a significant advantage of IAsp over RHI with respect to HbA1c reduction (WMD, –0.11%; 95% CI, –0.16 to –0.05; WMD, –1.2 mmol/mol; 95% CI, –1.7 to –0.5), with no evidence for between-study heterogeneity (P = 0.59; I2 = 0%) (FIGURE 2).

Postmeal glucose Four RCTs reported the level of postprandial blood glucose after individual daily meals and provided numerical data required for a meta-analysis. 23,27,29-31 Pooled results demonstrated an advantage of IAsp over RHI with respect to the postprandial glucose level, which was measured 90 minutes following each meal, including breakfast (WMD, –1.40 mmol/l; 95% CI, –1.72 to –1.07), lunch (WMD, –1.01 mmol/l; 95% CI, –1.61 to –0.41), and dinner (WMD, –0.89 mmol/l; 95% CI, –1.19 to –0.59). Statistical heterogeneity was observed in the meta-analysis for glycemic control following lunch (P = 0.04; I2 = 69%), however, this could be associated with a relatively low number of the included trials. No statistical heterogeneity was demonstrated in the remaining meta-analyses (FIGURES 3, 4, and 5).

Hypoglycemia None of the identified studies reported the number of patients with at least 1 hypoglycemic episode regardless of their severity. The risk of severe hypoglycemia requiring third-party assistance was assessed in 5 RCTs presenting data pertinent for meta-analysis. 21,24,26,29,31

Pooled results demonstrated a comparable risk of severe hypoglycemia between treatment groups (RR = 0.85; 95% CI, 0.66–1.08). Four RCTs reported the risk of nocturnal hypoglycemia, of which 2 studies reported a significantly lower risk of events in the IAsp group, while in 2 others, the between-group differences were not significant. 21,26,29,30 A meta-analysis of all studies confirmed a lower risk of nocturnal hypoglycemia in patients receiving IAsp compared with their counterparts treated with RHI (RR = 0.76; 95% CI, 0.64–0.91), with no evidence for between-study heterogeneity (P = 0.13, I2 = 46%).

Patients with type 2 diabetes mellitus Study characteristics A total number of 5 RCTs comparing IAsp with RHI in an overall number of 451 adult patients with T2DM were identified (FIGURE 1). 22-26

The mean duration of diabetes ranged from 4.6 to 17.5 years in respective trials, while the mean HbA1c at baseline was in the range of 7.3% (56 mmol/mol) to 8.7% (72 mmol/mol). Only in 1 study, the mean baseline body mass index exceeded 30 kg/m2, suggesting obesity in the majority of the subjects. 22 Two RCTs recruited T2DM patients who were previously treated with insulin, 22,26 two others enrolled insulin-naive subjects, 33,35 and
In 4 of the included studies, patients received intensive insulin treatment by MDI, while the remaining RCT compared IAsp with RHI, both administered twice daily together with OADs, but without the use of basal insulin. In 2 RCTs, all recruited patients received NPH as basal insulin, and in the other, participants were treated with either NPH or insulin detemir. In another RCT, the type of basal insulin was not reported.

### Table 1

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>IAsp n</th>
<th>IAsp mean (SD)</th>
<th>RHI n</th>
<th>RHI mean (SD)</th>
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<th>Weight, %</th>
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<td><strong>100.00</strong></td>
<td><strong>1.40 (-1.72 to -1.07)</strong></td>
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Total test for heterogeneity: $Q = 6.41, df = 3 (P = 0.05482), I^2 = 68.81%$

Test overall effect: $Z = -3.32 (P < 0.0001)$

### Table 2

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<td>7.56 (4.07)</td>
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<tr>
<td>Tamás, 2001</td>
<td>213</td>
<td>8.20 (4.38)</td>
<td>213</td>
<td>9.30 (4.38)</td>
<td>12.93</td>
<td>1.10 (-1.93 to -0.27)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>1.01 (-1.61 to -0.41)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total test for heterogeneity: $Q = 5.27, df = 3 (P = 0.1527), I^2 = 43.13%$

Test overall effect: $Z = -5.83 (P < 0.0001)$

### Table 3

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>IAsp n</th>
<th>IAsp mean (SD)</th>
<th>RHI n</th>
<th>RHI mean (SD)</th>
<th>WMD (95% CI)</th>
<th>Weight, %</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeVries, 2003</td>
<td>184</td>
<td>8.34 (4.34)</td>
<td>178</td>
<td>9.14 (3.87)</td>
<td>13.77</td>
<td>1.69 (-2.51 to -0.87)</td>
<td></td>
</tr>
<tr>
<td>Raskin, 2000</td>
<td>555</td>
<td>8.50 (4.06)</td>
<td>258</td>
<td>9.33 (3.66)</td>
<td>28.53</td>
<td>0.83 (-1.39 to -0.27)</td>
<td></td>
</tr>
<tr>
<td>Home, 2000</td>
<td>698</td>
<td>-</td>
<td>349</td>
<td>-</td>
<td>12.93</td>
<td>1.10 (-1.93 to -0.27)</td>
<td></td>
</tr>
<tr>
<td>Tamás, 2001</td>
<td>213</td>
<td>8.20 (4.38)</td>
<td>213</td>
<td>9.30 (4.38)</td>
<td>45.17</td>
<td>0.63 (-1.07 to -0.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.89 (-1.19 to -0.59)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total test for heterogeneity: $Q = 1.65, df = 3 (P = 0.65482), I^2 = 0.00%$

Test overall effect: $Z = -8.43 (P < 0.0001)$

These findings indicate that IAsp may be a viable alternative to RHI in the treatment of type 1 diabetes, as it offers comparable or superior glycemic control with fewer hypoglycemic episodes. Further research is needed to fully understand the long-term benefits and risks of IAsp therapy.
Hypoglycemia Two RCTs assessed the proportion of patients with at least 1 hypoglycemic episode during study treatment, regardless of severity. Pooled results demonstrated no significant between-group differences in the risk of overall hypoglycemia (RR, 1.00 [0.70–1.44]). Of 2 RCTs assessing the risk of severe hypoglycemia, one recorded no events in either group, while the other reported no significant difference between the study arms.

Neither study reported the risk of nocturnal hypoglycemia.

DISCUSSION In this systematic review, we compared the efficacy and safety of IAsp and RHI in T1DM and T2DM patients receiving prandial insulin therapy. Some evidence for IAsp superiority was identified. First, our meta-analysis demonstrated that IAsp compared with RHI in patients with T1DM provided favorable glycemic control, as assessed by HbA1c levels. It also reduced glucose fluctuations following all 3 major daily meals. At the same time, IAsp substantially reduced the risk of nocturnal hypoglycemia compared with RHI and demonstrated a comparable safety profile with respect to the risk of overall and severe hypoglycemic events. The estimates
of clinical efficacy of IAsp in patients with T1DM are highly consistent with our previous findings\textsuperscript{18} and the results presented by other authors.\textsuperscript{37-39} Additionally, we demonstrated a higher efficacy of IAsp over RHI in terms of HbA\textsubscript{1c} reduction in patients with T2DM treated with prandial insulin. This is a new finding, which has not been presented in any previous systematic reviews or meta-analysis.

We believe that the above findings were possible owing to novel evidence and improved methodological quality. For example, in our former meta-analysis, we adopted relatively less stringent criteria allowing for the inclusion of studies with relatively high degrees of heterogeneity with respect to population, intervention, and methodology. This high between-study variation, particularly the inclusion of studies with biphasic insulin in the same meta-analysis with RCTs assessing IAsp, along with an insufficient number of relevant RCTs available at that time, were the main reasons why we were unable to demonstrate superiority of IAsp over RHI in T2DM. In the current report, we included new studies, which were published since 2010 and, therefore, could not be considered in older reports.\textsuperscript{24,33,34} One of these new studies enrolled children with T1DM,\textsuperscript{24} while 2 others were carried out in patients with T2DM.\textsuperscript{23,34} The inclusion of new evidence allowed us to use more rigid criteria in order to improve the credibility of evidence by ensuring an appropriate level of between-study homogeneity, particularly in the population with T2DM, where data availability has been limited so far. Indeed, we excluded RCTs with a follow-up shorter than 12 weeks, which is a rational approach as the level of HbA\textsubscript{1c}, the primary endpoint of the current analysis, reflects changes in blood glucose over the period of the last 3 months. Moreover, this analysis was focused only on the assessment of the prandial insulin therapy (in all but 1 study, the intensive insulin therapy model was applied) that included IAsp; therefore, studies comparing biphasic insulin aspart with RHI were considered irrelevant. Finally, we also excluded studies enrolling solely pregnant women, analyzed in our previous work, as being not representative for the entire T1DM population. Altogether, the inclusion of new RCTs and the adoption of a more coherent methodology have led to reduced heterogeneity and improved precision of efficacy estimates. This allowed us to demonstrate a significant advantage of IAsp over RHI in glycemic control in both types of diabetes mellitus.

A recent meta-analysis based on individual patient data (IPD) included a total number of 10 RCTs comparing IAsp with RHI, both used in basal-bolus regimen together with NPH, in patients with T1DM (6 RCTs), T2DM (3 RCTs), or a mixed population of both types of diabetes (1 RCT).\textsuperscript{40} All trials were pooled together and no separate analysis for each diabetes type was performed. The results of the meta-analysis showed that IAsp reduced HbA\textsubscript{1c} by 0.1% (1.1 mmol/mol) as compared with RHI; this was accompanied by lower postprandial blood glucose levels. Consistent with our results for T1DM, the authors also demonstrated a lower risk of nocturnal hypoglycemia in the IAsp group; however, the overall proportion of patients experiencing hypoglycemic episodes was comparable in both arms. The high consistency of our results in T1DM and those presented by Heller et al.\textsuperscript{40} is of interest as the methodologies of both reports varied substantially. First, the other meta-analysis included solely trials with available IPD, of which some have not been published yet. Second, the authors decided to perform one single analysis for both types of diabetes presenting one single estimate, which could be the source of considerable heterogeneity. Finally, several available studies but with unavailable IPD were excluded from the analysis. Although a meta-analysis by Heller et al.\textsuperscript{40} was based on specific information, which could not be easily assessed, it provided valuable complementary and supportive data to our work.

Two milestone prospective diabetes studies, The UK Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT), demonstrated that more intensive therapies, although improving glycemic control, are almost inevitably associated with an increased risk of severe hypoglycemia.\textsuperscript{2,9} More recently, these results were confirmed by a meta-analysis of 67 RCTs showing that the degree of HbA\textsubscript{1c} reduction correlated with the risk of overall, severe, and nocturnal hypoglycemia.\textsuperscript{41} Therefore, hypoglycemia is often considered a barrier for effective glycemic control. Interestingly, our results demonstrated that IAsp as compared with RHI allows for better glycemic control without an increased risk of hypoglycemia; moreover, a decreased risk of nocturnal events was observed in the T1DM cohort. This phenomenon can probably be attributed to the favorable pharmacokinetic properties of IAsp, which provide very short-acting activity and, thus, limit the risk of late falls in glucose levels.\textsuperscript{17} IAsp also allows for a more precise adjustment of the insulin concentration in response to an increase in blood glucose levels following daily meal intake, which is reflected in a higher clinical efficacy with respect to postprandial glucose control. These properties are of clinical value because postprandial glucose fluctuations contribute to 52% to 59% of total hyperglycemia in patients with intensified therapy for T2DM.\textsuperscript{42}

Unlike IAsp, the activity of RHI is still significant several hours after the injection, which predisposes a patient to hypoglycemia, particularly during the night. Nocturnal hypoglycemia is frequent in patients treated with insulin, and although it usually has an asymptomatic course it may lead to significant clinical consequences, including sudden death.\textsuperscript{43,44} As reported by the DCCT trial, 55% of all severe hypoglycemic events occur during the night.\textsuperscript{45} Patients who once experienced nocturnal hypoglycemia tend to reduce their adherence to insulin treatment or
even intentionally reduce their insulin dose.\textsuperscript{16,17} Therefore, IAsp may provide particular clinical benefit in patients at risk of nocturnal hypoglycemia, especially those with T1DM.

Important limitations of our report include the low quality of most studies identified within this systematic review. Some RCTs were only presented in an abstract form without a subsequent presentation in full-text publications, which limits the availability of the data required for credibility assessment.\textsuperscript{21,25,26} Between-study variability in insulin regimen, duration of intervention period and study design could also potentially confound the results of our meta-analysis. These limitations are inherent problems of most secondary studies in diabetes that attempt quantitative data synthesis; therefore, the results of the current and other meta-analyses should be interpreted with caution and revised when new evidence becomes available.

In summary, IAsp demonstrates better glycemic control with respect to HbA1c, and prandial glucose fluctuations compared with RHI in patients with both T1DM and T2DM receiving a prandial insulin regimen therapy. Additionally, IAsp is associated with fewer nocturnal hypoglycemic events in the T1DM population and has a comparable safety profile with respect to severe hypoglycemia in all patients, regardless of the type of diabetes mellitus.

**Contribution statement** PW, PN-S, PJ, BM, JS-D, PR, and MTM developed the protocol; PN-S, EO searched medical databases and extracted the data; PW and PN-S analyzed the data; PW, PR, and MTM wrote the manuscript; MTM, BM, and JS-D made a critical review of the manuscript. All authors approved the final version of the manuscript. MTM and PR coordinated the project.

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**REFERENCES**


ARTYKUŁ ORYGINALNY

Efektywność kliniczna i bezpieczeństwo stosowania insuliny aspart w porównaniu z insuliną ludzką u pacjentów z cukrzycą typu 1 oraz 2 – przegląd systematyczny i metaanaliza

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⁴ Szpital Uniwersytecki, Kraków, Polska

SŁOWA KŁUCZOWE

analogi szybko działające insuliny, cukrzyca typu 1, cukrzyca typu 2, insulina aspart, insulinoterapia

STRESZCZENIE

Insulina posilkowa stanowi kluczową komponentę insulinoterapii w cukrzycy typu 1 (type 1 diabetes mellitus – T1DM) i w wielu pacjentów z cukrzycą typu 2 (type 2 diabetes mellitus – T2DM). Dane oparte na dowodach naukowych wspierające wybór preparatu insulinowego są w dalszym ciągu nieliczne.

CELE
Przeprowadziliśmy przegląd systematyczny w celu podsumowania i aktualizacji dowodów naukowych dotyczących względnej skuteczności i bezpieczeństwa stosowania insuliny aspart (IAsp) oraz insuliny ludzkiej (regular human insulin – RHI) w obydwu typach cukrzycy.

METODY
Randomizowane badania kliniczne porównujące IAsp z RHI u pacjentów z T1DM lub T2DM przeprowadzone w okresie do maja 2013 roku znaleziono w ramach przeszukiwania systematycznego baz MEDLINE, EMBASE i Cochrane Library.

WYNIKI
Z 16 znalezionych badań 11 dotyczyło pacjentów z T1DM, a 5 – pacjentów z T2DM. W populacji z T1DM IAsp w porównaniu z RHI zapewniał większą redukcję poziomu HbA₁c (różnica średnich ważonych [weighted mean difference – WMD] –0,11%; 95% CI: od –0,16 do –0,05; WMD –1,2 mmol/mol; 95% CI od –1,7 do –0,5) i lepszy poziom glikemii poposiłkowej mierzony po: śniadaniu (WMD –1,40 mmol/l; 95% CI: od –1,72 do –1,07), obiedzie (WMD –1,01 mmol/l; 95% CI: od –1,61 do –0,41) i kolacji (WMD –0,89 mmol/l; 95% CI: od –1,19 do –0,59). Ryzyko nocnej hipoglikemii było niższe u pacjentów z T1DM otrzymujących IAsp (RR 0,76; 95% CI: 0,6–0,91), natomiast w przypadku ciężkiej hipoglikemii nie obserwowano różnic pomiędzy grupami. U pacjentów z T2DM stosowanie IAsp prowadziło do większej redukcji poziomu HbA₁c (WMD –0,22%; 95% CI: od –0,39 do –0,05; WMD –2,4 mmol/mol; 95% CI: od –4,3 do –0,5) oraz glikemii poposiłkowej. Ryzyko wystąpienia hipoglikemii ogółem oraz poważnych zdarzeń niepożądanych było porównywalne w obu badanych grupach.

WNIOSKI
W porównaniu z RHI IAsp zapewnia lepszą kontrolę glikemii u chorych z T1DM oraz T2DM. Mniej pacjentów z T1DM leczonych IAsp doświadczano hipoglikemii nocnych, podczas gdy w przypadku obu interwencji ryzyko ciężkiej hipoglikemii było porównywalne dla obu typów cukrzycy.