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The Use of Technosphere Insulin (Afrezza) and Ultra-Rapid Insulins in the Treatment of Type 1 Diabetes Mellitus: A Systematic Review

Iapunira Catarina Sant'Anna Aragão[1], Felipe Matheus Sant'Anna Aragão[2], Marcelo Lucas de Lima Prado[3], Marlon Nunes Barreto da Silva[4], Vera Lúcia Corrêa Feitosa[5], Francisco Prado Reis[6], José Aderval Aragão[7]*

[1]On-Call Physician at São Lucas Hospital with a specialization in Internal Medicine. Av. Avelino Batista Soares, nº 297 – Centro – Quatis – RJ, Brazil

[2]Cardiology Resident at the Heart Institute of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo (INCOR), Av. Dr. Enéas Carvalho de Aguiar, 44 - Cerqueira César, São Paulo - SP, Brazil

[3]Medical Student, Department of Medicine, Federal University of Sergipe (UFS), Aracaju, SE, Brazil. Avenida Marechal Rondon, S/N, Rosa Elze, São Cristóvão – SE, Brazil

[4]Medical Student, Department of Medicine, Federal University of Sergipe (UFS), Aracaju, SE, Brazil. Avenida Marechal Rondon, S/N, Rosa Elze, São Cristóvão – SE, Brazil

[5]Titular Professor of Cell Biology, Department of Morphology, Federal University of Sergipe (UFS), Aracaju, Sergipe, Brazil. Avenida Marechal Rondon, S/N, Rosa Elze, São Cristóvão – SE, Brazil

[6]Titular Professor, Medical School of Tiradentes University (UNIT), Aracaju, SE, Brazil. Av. Murilo Dantas, 300, Farolândia, Aracaju – SE, Brazil

[7]Titular Professor of Clinical Anatomy, Department of Morphology, Federal University of Sergipe (UFS), Avenida Marechal Rondon, S/N, Rosa Elze, São Cristóvão – SE, Brazil

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***Corresponding author:** José Aderval Aragão, Department of Morphology, Federal University of Sergipe, Center of Biological and Health Sciences, Campus Cidade Universitária Professor José Aloísio de Campos, São Cristóvão, Sergipe, Brazil

Abstract

We aim to evaluate the efficacy and safety of Technosphere insulin (Afrezza) and ultra-rapid insulins in the treatment of Type 1 Diabetes Mellitus. The research compares the efficacy of these insulins with traditional therapies, focusing on reductions in glycated hemoglobin levels and hypoglycemic episodes, and on body weight control. This systematic review followed PRISMA guidelines and searched the PubMed, SciELO, and LILACS databases. Two independent reviewers assessed the methodological quality of included studies using the Cochrane RoB 2 tool. The main findings indicate that ultra-rapid insulins and Technosphere insulin provided effective glycemic control, reduced glycated hemoglobin, decreased hypoglycemia, and maintained body weight. Associated technologies, such as insulin pumps, also showed promise in managing the disease. Studies suggest that these insulins improve glycemic control, especially postprandially. However, further research is needed to optimize safety and personalize treatment, particularly in high-risk patients.

Keywords: Ultra-Rapid Insulins; Type 1 Diabetes Mellitus; Glycated Hemoglobin; Hypoglycemia

Abbreviations: T1DM: Type 1 Diabetes Mellitus; HbA1c: Glycated hemoglobin; FIA: Fast insulin aspart; SIA: Standard insulin aspart; URLi: Ultra rapid Lispro; CLC: Automated closed-loop control; SAP: Sensor-augmented insulin pump; PPG:Postprandial glucose test; DBGL1: Diabeloop Generation 1

INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic condition resulting from the autoimmune destruction of pancreatic beta cells, leading to an absolute insulin deficiency [1]. This autoimmune disease is predominantly observed in childhood and adolescence, being a major concern in pediatrics in Brazil. With a global prevalence that ranks T1DM third in incidence, it is estimated that approximately 51,500 children and adolescents, aged between 0 and 14 years, are affected in the country [2].

The onset of the autoimmune process is asymptomatic, with immunological and metabolic markers only becoming detectable after a prolonged period of cellular destruction [1]. According to Nurhakim et al. [3], the clinical manifestation of the disease occurs when the function of the remaining endocrine cells is no longer sufficient to maintain glycemia within physiological standards, resulting in symptoms such as weight loss, polydipsia, polyuria, and, in severe cases, diabetic ketoacidosis.

According to García [4], monitoring T1DM is a constant challenge, and glycated hemoglobin (HbA1c) is widely used as the gold standard for assessing glycemic control. This measure provides an estimate of the glycemic trend over the past three months, allowing an indirect view of the patient's metabolic control. However, HbA1c may have limitations in accuracy in conditions such as anemia, hemoglobinopathies, or chronic kidney disease, which can impact the assessment of glycemic control. The management of T1DM involves a delicate balance between insulin administration and monitoring of glycemic levels, and the accuracy of measurements is fundamental to the effectiveness of the treatment.

Studies by Vilela et al. [5] indicate that the treatment of T1DM has recently been revolutionized by technological advances in insulin administration. Rapid-acting insulins, such as Technosphere Insulin Afrezza®, represent an advance by mimicking the release of insulin bolus needed after meals. Afrezza® was approved by the FDA in June 2014 and by Anvisa in 2019, offering a new option for managing T1DM.

Given the above, this study aims to evaluate the efficacy and safety of using Afrezza and ultra-rapid insulins in the treatment of patients with Type 1 Diabetes Mellitus. The research focuses on determining whether these treatments offer optimized glycemic control and reduce complications compard to other traditional therapeutic approaches. Specifically, the study seeks to compare the efficacy of Afrezza with ultra-rapid insulins in reducing HbA1c levels and the incidence of hypoglycemia in patients with T1DM. This aspect is essential to understand how different types of insulin impact long-term glycemic control and patient safety, especially regarding the prevention of hypoglycemic episodes, which are common and potentially dangerous in this population. In addition, the study aims to evaluate the influence of using Technosphere Insulin (Afrezza) and ultra-rapid insulins on body weight maintenance in patients with Type 1 Diabetes Mellitus. This objective is important to investigate whether these therapeutic options have distinct effects on patients' weight, a relevant factor for the overall management of diabetes, as weight control is often associated with metabolic control and reduced risk of long-term complications.

METHODS

This systematic review was not registered a priori in the PROSPERO database. After obtaining the files with the references recovered from the databases, all stages of the systematic review were conducted in the Zotero tool. Furthermore, the methodology of this work was elaborated according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6].

Search Strategy

Three bibliographic databases were consulted: PubMed, SciELO, and Latin American and Caribbean Literature (LILACS). The search strategy included controlled descriptors: ((Technosphere Insulin OR Afrezza OR ultra-rapid insulin OR (ultra rapid insulin) OR (ultra-fast insulin) OR (ultra-fast insulin)) AND (HbA1c OR (glycated hemoglobin) OR (glycosylated hemoglobin) OR (A1C) OR (body weight) OR (body weight maintenance) OR (weight change) OR (weight management) OR hypoglycemia OR (hypoglycemic episodes) OR (low blood sugar)) AND (Type 1 Diabetes Mellitus OR (Type 1 Diabetes) OR (T1DM) OR (Diabetes Mellitus Type 1) OR (Type I Diabetes Mellitus))) AND ((treatment efficacy) OR (glycemic control) OR (blood glucose control) OR (HbA1c reduction) OR (basal-bolus regimen) OR (basal bolus) OR (insulin regimen)). The initial search in the databases occurred in August/2024, being subsequently updated in September/2024.

Eligibility Criteria

The inclusion criteria for this study encompass patients with T1DM who present relevant outcomes, such as HbA1c levels, body weight, or incidence of hypoglycemia. These patients should be young, adults, elderly, male, or female, and be included in studies that involve comparisons with ultra-rapid insulins. In addition, only studies that report the incidence of hypoglycemia and that are of the type randomized clinical trials, case-control studies, systematic reviews, or meta-analyses are considered. These studies must have been published in the last five years and be available in English, Portuguese, or Spanish.

Moreover, the exclusion criteria comprise studies where there is a predominance of patients with type 2 diabetes mellitus (DM2), the presence of health conditions that may confound the results, or that use different forms of insulin. Also excluded are single-case studies, case reports, studies without a comparator group, or that do not evaluate outcomes such as HbA1c, hypoglycemia, or body weight. In addition, studies published in non-permitted languages or more than five years ago are not considered eligible for the analysis.

Evaluation by Title and Abstract, Full Reading, and Data Extraction

After importing the files containing the bibliographic references to the Zotero tool, the first step of the work consisted of verifying duplicates, both within each database and between them. Then, two researchers independently evaluated the titles and abstracts of the articles recovered in the bibliographic databases. The articles selected in this phase were submitted to full reading,

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also with independent evaluation in duplicate. However, in this last step, any disagreements were resolved by a third reviewer. After full reading, the articles that met all the eligibility criteria were submitted to an evaluation of methodological quality and had their data extracted. The narrative synthesis was structured from the data on the year of publication, author, article title, synthesis of the abstract, objectives, synthesis of the methodology, main results, and synthesis of the conclusions.

Evaluation of Methodological Quality

The methodological quality of the studies was evaluated by two independent researchers, using the Cochrane tool for randomized trials (RoB 2). RoB2 classifies the quality of bias of the studies as "high," "some concerns," and "low," representing, in increasing order, the susceptibility to biases that may compromise the validity of the information produced.

This instrument is applicable for different types of research designs and is composed of six components: (1) Randomization process, (2) Deviations from interventions (3) Missing outcome data (4) Measurement of the outcome (5) Selection of the reported outcome, and (6) General. Methodological doubts and disagreements between the evaluations, in both instruments, were resolved by a third researcher. And, no statistical analyses were performed.

RESULTS

From 249 potentially relevant articles identified, where 3 were identified as duplicates and excluded, 89 publications were read in full, of which 22 met the eligibility criteria and were included in the narrative synthesis. The flowchart of study selection is presented in [Figure 1].

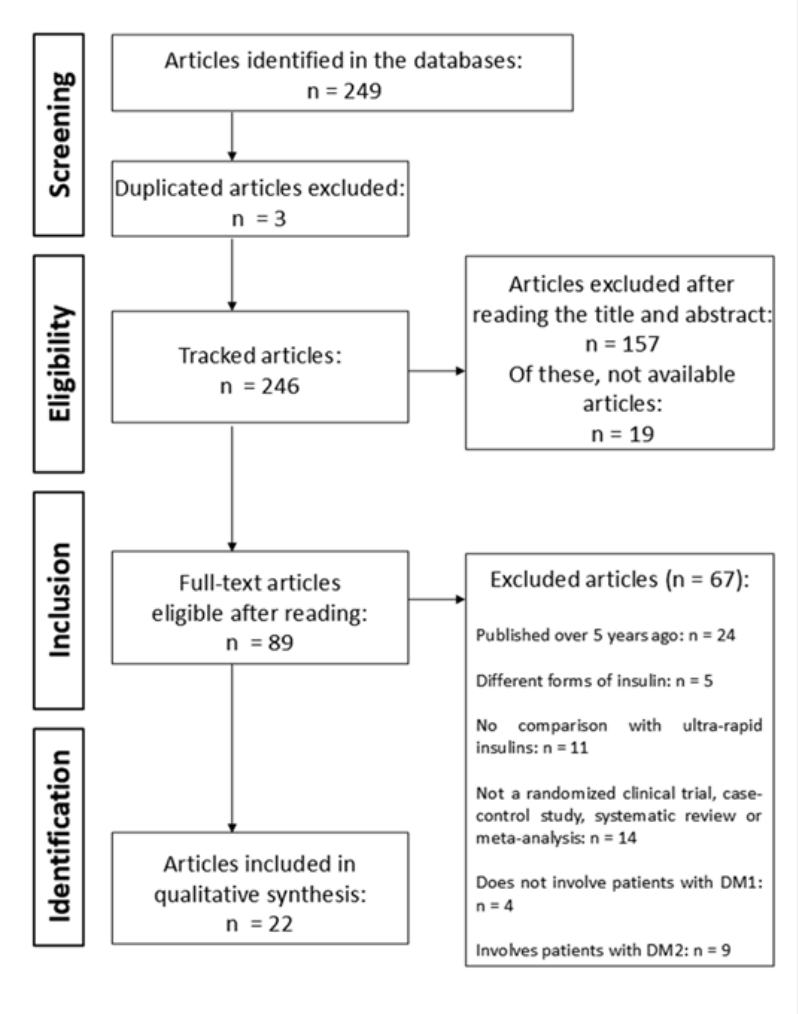

Figure 1: Flowchart of the study selection process.

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The general characteristics of the selected studies are described in [Table 2]. The number of participants ranged from 10 to 716 individuals, including children, adolescents, and adults, in studies involving type 1 diabetes. The highest frequency was observed among adult patients, with emphasis on individuals in automated insulin therapy regimens and associated technologies, such as the use of insulin pumps and closed-loop systems. Most studies included participants with type 1 diabetes who were evaluating new therapies or modalities of glycemic control, such as hybrid closed-loop systems and the use of different insulin formulations. Regarding the type of study design, the randomized clinical trial predominated, with formats varying between phase 1 to phase 3, with some studies being multicenter and crossover, such as those by Leohr et al. [7], Ma et al. [8], and Wadwa et al. [9]. In addition, some studies also performed post hoc analyses, such as that by Benhamou et al. [10]. The follow-up time varied, depending on the modality investigated, with a focus on new approaches for insulin administration and glycemic control, as observed in the study by AlGhatam et al. [11], which analyzed the impact of advanced insulin pump settings during Ramadan (Table2).

In [Table 1], the results of the methodological quality assessment of the analyzed works are described. According to the Cochrane instrument (RoB 2), eighteen studies (81.82%) were classified with "low" risk of bias, four (18.18%) with "some concerns," and zero (0%) with "high." Based on the assessment instrument, the main factor for downgrading in the level of bias in the research was related to high rates of losses and dropouts during follow-up (or the absence of reporting this information) and the fragility in the sample selection bias, which compromised the ability to generalize the results. In addition, a characteristic of studies with lower methodological quality was the lack of adjustments in the analyses for possible confounding factors.

Table 1: Evaluation of the methodological quality of the articles included in the review according to the Cochrane tool for randomized trials (RoB 2).

Domain → Study ↓	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported outcome	General
Dovc et al. [12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Garcia-Tirado et al. [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
McCarthy et al. [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Garcia-Tirado et al. [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bode et al. [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
AlGhatam et al. [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dutta et al. [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wadwa et al. [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kovatchev et al. [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Renard et al. [19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Owens et al. [20]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Leohr et al. [7]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Klaff et al. [21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Miura et al. [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ma et al. [8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Malecki et al. [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Evans et al. [24]	Some concerns	Some concerns	High risk	Some concerns	Some concerns	Some concerns
Benhamou et al. [10]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Von dem Berge et al. [25]	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk
Pinsker et al. [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
McGill et al. [27]	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk
Mauras et al. [28]	Low risk	Low risk	High risk	High risk	Low risk	Some concerns

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Table 2: Main results found in the selected studies.

Authors	Main Findings	Themes
Dovc et al. [12]	Study type: Randomized, double-blind, crossover clinical trial. Characteristics: 30 young participants with type 1 diabetes using FIA or SIA. Conclusion: FIA was not superior to SIA in the use of the AID system.	Comparison of Insulin Types
Wadwa et al. [9]	Study type: Randomized, multicenter study. Characteristics: 716 children and adolescents with type 1 diabetes comparing URLi and lispro. Conclusion: URLi is effective and safe for pediatric use.	
Dutta et al. [17]	Study type: Randomized, parallel, multicenter clinical trial. Characteristics: 127 participants with type 1 diabetes comparing CLC with SAP. Conclusion: CLC is a viable approach for the treatment of type 1 diabetes.	
Owens et al. [20]	Study type: Review of phase 1 and phase 3 clinical trials. Characteristics: Second-generation insulin analogs. Conclusion: New insulin analogs offer better postprandial glycemic control.	
Leohr et al. [7]	Study type: Randomized, phase 1, crossover, double-blind clinical trial. Characteristics: 32 adult participants with type 1 diabetes comparing URLi and Humalog. Conclusion: URLi provides faster recovery from hyperglycemia.	
Ma et al. [8]	Study type: Multicenter, randomized, double-blind, phase 3 study. Characteristics: 354 predominantly Chinese patients with type 1 diabetes. Conclusion: URLi is superior to insulin lispro in controlling PPG.	
Miura et al. [22]	Study type: Randomized, phase 3, double-blind clinical trial. Characteristics: 167 Japanese patients with type 1 diabetes comparing URLi and lispro. Conclusion: URLi provides effective glycemic control.	
Evans et al.[24]	Study type: Review. Characteristics: Use of rapid-acting insulin aspart in insulin pump therapy. Conclusion: Faster aspart provides better postprandial control than conventional aspart insulin.	
Malecki et al. [23]	Study type: Randomized, phase 3, double-blind study. Characteristics: 269 patients with type 1 diabetes comparing URLi and lispro. Conclusion: URLi showed to be superior to lispro in PPG control and time in target glucose range.	
McCarthy et al. [14]	Study type: Randomized, crossover clinical trial. Characteristics: 10 adults with type 1 diabetes, using the MiniMed 780G system during exercise. Conclusion: Prudent preparation and pre-planned insulin management are necessary.	
Kovatchev et al. [18]	Study type: Randomized, parallel, multicenter clinical trial. Characteristics: 127 participants with type 1 diabetes comparing CLC with SAP. Conclusion: CLC is a viable approach for the treatment of type 1 diabetes.	Efficacy and Safety of New Insulin Formulations
Renard et al. [19]	Study type: Randomized, parallel, multicenter clinical trial. Characteristics: 72 adults with type 1 diabetes at high risk of hypoglycemia. Conclusion: AID is safe and effective in reducing the risk of hypoglycemia.	
Benhamou et al. [10]	Study type: Post hoc analysis of three randomized clinical trials. Characteristics: Patients with T1DM using DBLG1 hybrid closed-loop system. Conclusion: The DBLG1 system is safe and effective in reducing time in hypoglycemia.	
Von dem Berge et al. [25]	Study type: Randomized, controlled, crossover study. Characteristics: 38 children aged 2 to 14 years using different treatment modalities. Conclusion: The hybrid closed-loop system improves glycemic control in children.	
Pinsker et al. [26]	Study type: Randomized, crossover study. Characteristics: 35 participants with DM1 using AID and SAP. Conclusion: Weekly adaptation of AID reduced time in hypoglycemia.	
Mauras et al. [28]	Study type: Randomized study. Characteristics: 295 participants with DM1 using BP-generated backup insulin regimens. Conclusion: The BP-generated backup insulin regimen can be implemented safely.	
Bode et al. [16]	Study type: Phase 3, randomized, double-blind, crossover study. Characteristics: 49 adult patients with type 1 diabetes using URLi or lispro. Conclusion: URLi was compatible and showed a trend towards better glycemic control.	
McGill et al. [27]	Study type: Randomized, open-label clinical trial. Characteristics: 138 participants with DM1 comparing TI and LIS. Conclusion: Inhaled TI offers comparable glycemic control to LIS with a lower risk of hypoglycemia.	

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Garcia-Tirado et al. [13]	Study type: Randomized and crossover clinical trial. Characteristics: 35 adults with type 1 diabetes, comparing three modalities of AID systems. Conclusion: Meal anticipation did not improve postprandial control.	Impact of Specific Context on Insulin Administration
AlGhatam et al. [11]	Study type: Randomized pilot study. Characteristics: 30 patients with type 1 diabetes during Ramadan. Conclusion: The use of advanced insulin pump settings improves glycemic control.	
Garcia-Tirado et al. [15]	Study type: Randomized, controlled, and crossover clinical trial. Characteristics: 35 adults with type 1 diabetes, receiving empagliflozin or not. Conclusion: The addition of empagliflozin improved daytime glycemic control.	Integration of Adjuvant Therapies with Insulin

DISCUSSION

Comparison of Insulin Types

According to the study by Wadwa et al. [9], ultra-rapid lispro insulin (URLi) was shown to be non-inferior to lispro in terms of HbA1c control, with additional benefits in reducing postprandial glucose (PPG) when administered at mealtime. Dutta et al. [12] also confirmed that URLi and lispro have similar safety profiles, although the use of rapid-acting lispro has been associated with an increase in injection site reactions. Both studies highlight the efficacy and safety of ultra-rapid lispro insulin compared to standard lispro, suggesting that ultra-rapid insulin offers superior postprandial glycemic control without compromising safety, making it an effective therapeutic option for both children and adults with diabetes.

Now, when comparing the different types of insulin, it is possible to observe in the studies by Miura et al. [13] and Malecki et al. [14], which also compared URLi with lispro, that ultra-rapid insulin improves postprandial glycemic control and increases the time within the target glucose range. Miura et al. [13] focused on the Japanese population, highlighting specific responses to URLi, while Malecki et al. [14] used continuous glucose monitoring (CGM) for detailed data on postprandial glycemic control over 26 weeks. Both studies showed that rapid-acting lispro administered before meals is superior in reducing postprandial glucose excursions and increasing time in range (TIR). However, the administration of URLi after meals was less effective, suggesting that the timing of administration is essential for optimal glycemic control. In addition, aiming to identify other ultra-rapid insulins, the studies by Dovc et al. [15] and Evans et al. [16] analyzed the efficacy of faster-acting insulin aspart (faster aspart) compared to conventional aspart. Dovc et al. [15] highlight its faster absorption and better immediate postprandial glycemic control. Evans et al. [16] complement this by showing that, although not superior in reducing HbA1c, faster aspart is more effective in post-meal glycemic control in pump therapy (CSII). Both studies emphasize the importance of personalized adjustments in pumps when using faster aspart, suggesting frequent monitoring and fine adjustments to optimize diabetes management.

Thus, among the three types of insulin – URLi, conventional Lispro, and faster-acting insulin aspart – URLi stands out as the most effective in controlling postprandial glycemia. Studies by Wadwa et al. [9] and Dutta et al. [12] showed that rapid-acting Lispro offers superior glycemic control to conventional Lispro, especially when administered before meals, reducing postprandial glucose without compromising safety, although associated with a slight increase in injection site reactions. The study by Malecki et al. [14] highlighted that ultra-rapid insulin provides greater time within the target glucose range (TIR), indicative of better daytime control, compared to conventional Lispro. Faster aspart insulin also showed faster absorption and effective postprandial glycemic control, especially with continuous subcutaneous insulin infusion (CSII), according to Dovc et al. [15] and Evans et al. [16]. However, personalized dose adjustments may be necessary. Although faster aspart has advantages in specific contexts, URLi, with its balanced profile between efficacy and convenience, emerges as the best option for postprandial management in the control of type 1 diabetes.

Automated Insulin Delivery Technologies

The studies by McCarthy et al. [17], Renard et al. [18], and Pinsker et al. [19] analyze automated insulin delivery (AID) systems in different scenarios, highlighting advances and challenges in the management of type 1 diabetes. McCarthy et al. [17] demonstrate that, in situations of physical exercise, prior preparation with insulin adjustments can minimize hypoglycemia, highlighting the importance of calibration in contexts of high glycemic variability. Renard et al. [18] complement these findings by showing that AID reduces time in hypoglycemia in high-risk patients. Pinsker et al. [19] discuss the automatic adaptation of insulin parameters in AID, pointing out that, despite reducing hypoglycemia, there is room for improvement in the algorithms, especially in well-controlled populations. Comparison with the other two studies suggests that, while prior adjustment strategies, such as those used in exercise, are effective in contexts of immediate risk, automated adaptation in everyday life may face limitations in well-controlled populations. Thus, together, the three studies complement each other by showing that, although AID offers advances, personalization and the specific context of use are essential to optimize results and improve glycemic control.

Furthermore, when comparing the studies by Kovatchev et al. [20], Benhamou et al. [21], Von dem Berge et al. [22], and Mauras et al. [23] on automated insulin delivery systems, it reveals a continuous evolution in the management of type 1 diabetes,

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highlighting improvements in various glycemic control metrics. All articles highlight the increase in time in range (TIR) and the reduction in time in hypoglycemia, albeit with distinct focuses and populations. The study by Benhamou et al. [21] analyzes the DBLG1 system in patients with excessive time in hypoglycemia, demonstrating a reduction in time below 70 mg/dL, with emphasis on the 5.1% improvement in TIR and a reduction of more than 50% in time in hypoglycemia. This focus on high-risk patients complements the study by Mauras et al. [23], which examines the use of the bionic pancreas and its insulin backup system, confirming that such devices maintain safety and efficacy, even in unexpected transitions, which is essential for patients with a greater propensity for hypoglycemia. In contrast, the study by Von dem Berge et al. [22] reveals that preschool and school-age children also benefit greatly from AID, achieving improvements in TIR of up to 15% with the use of the hybrid closed-loop system. And, when complementing with the Benhamou study [21], we see that AID is effective both in pediatric populations and in high-risk adult patients. The study by Kovatchev et al. [20], in turn, demonstrates that the use of mobile closed-loop systems, such as in control, can reduce time in hypoglycemia with a more flexible and integrated approach. These complementary findings suggest that, regardless of the population — children, adults, or individuals at high risk of hypoglycemia — AID systems improve glycemic control and safety, with emphasis on the personalization of algorithms and the continuity of treatment, even in critical situations.

Efficacy and Safety of New Insulin Formulations

When comparing the studies by Bode et al. [24] and McGill et al. [25], it is possible to perceive that the authors address new strategies to improve glycemic control in patients with type 1 diabetes, using different forms of insulin administration. Bode et al. [24] analyze URLi in continuous subcutaneous infusion, showing that it improves postprandial glycemic control compared to conventional Lispro, with an increase in time within the target range. Despite mild reactions at the insertion site that led to premature changes in the infusion sets, URLi was considered safe and effective in continuous infusion pumps. On the other hand, McGill et al. [25] explore Technosphere Inhaled Insulin (TI), which demonstrated a faster glycemic response in the first 90 minutes after meals and reduced mild or moderate hypoglycemia events compared to injectable Lispro. TI allowed greater flexibility in diabetes management due to its rapid absorption and short duration of action, although it presented mild adverse events, such as cough. With this, it is noted that both studies contribute to the treatment of type 1 diabetes, offering effective alternatives to improve glycemic control. While URLi stands out in continuous infusion, providing predictability in postprandial control, TI offers an innovative and less invasive option with administration by inhalation, benefiting patients who prefer to avoid injections. These two approaches broaden therapeutic options, allowing for more personalized diabetes management.

Impact of Specific Context on Insulin Administration

According to the studies by Garcia-Tirado et al. [26] and AlGhatam et al. [27], it is observed that the authors provide different perspectives on the improvement in insulin delivery for patients with Type 1 Diabetes, although they approach the topic from different angles. The first article focuses on meal anticipation in fully automated insulin delivery systems. It highlights that, while the hybrid closed-loop system (HCL) offered better post-breakfast control with 74% time in range (TIR), total closed-loop systems (FCL and FCL+ with meal anticipation) still maintained over 70% TIR. The study also revealed that meal anticipation did not increase the risk of hypoglycemia, even when meals were delayed. These findings suggest that, although meal anticipation systems may not dramatically improve postprandial control, they maintain safety and glycemic control.

On the other hand, the study by AlGhatam et al. [27] explores insulin pump adjustments during Ramadan fasting. It compared different features of insulin pumps, such as temporary basal rates (TBR) and extended bolus (EB), among patients who fast during Ramadan. The intervention group that used these features showed an improvement in TIR, from 63% to 76%, indicating that personalized pump adjustments can effectively improve glycemic control during fasting. Unlike the meal anticipation study, which found little difference in postprandial outcomes, this study highlights the benefits of using advanced pump features to manage glucose patterns induced by fasting, particularly reducing hyperglycemia after meals. Thus, it was possible to perceive that both studies emphasize the importance of technological advances in insulin administration, but while meal anticipation systems seem more focused on safety during delays, the advanced features of pumps show greater effectiveness in controlling glycemic fluctuations induced by fasting.

Integration of Adjuvant Therapies with Insulin

The study by Garcia-Tirado et al. [28] investigated the impact of adding empagliflozin (EMPA) to AID delivery systems and predictive low-glucose suspend (PLGS) in patients with type 1 diabetes. The combination of 5 mg daily of EMPA with AID increased the time in the glycemic target range from 71% to 81%, with no increase in the risk of hypoglycemia, but with one episode of diabetic ketoacidosis (DKA) recorded. With PLGS, the TIR increased from 63% to 80%. Despite the glycemic benefits, the study highlights the need for strategies to mitigate the risk of DKA in future trials.

CONCLUSION

The conclusion of this study demonstrates that automated insulin delivery, such as Technosphere Insulin (Afrezza) and ultra-rapid insulins, is a promising solution for the treatment of Type 1 Diabetes Mellitus, offering better postprandial glycemic control without increasing the risk of hypoglycemia. Despite the effectiveness of insulin pumps and closed-loop systems, further

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research is needed to optimize safety and efficacy, especially in high-risk groups. The review also points out that these technologies reduce glycated hemoglobin, maintain body weight, and prevent long-term complications. It is concluded that ultra-rapid insulin systems and new technologies are valuable tools, but their success depends on the personalization of algorithms and continuous patient monitoring.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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