

Systematic Review of Oral Carbohydrate Treatment for Non-Severe Hypoglycemia in Type 1 Diabetes: A Comparison of Insulin Management Systems

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Abstract: The general recommendation for hypoglycemia treatment is 15 grams (g) of simple carbohydrates, with re-check in 15 minutes. This oral hypoglycemia treatment is universally applied without consideration of the type of diabetes or the cause of hypoglycemia. These recommendations were only based on two small-sized studies of intravenous insulin-induced hypoglycemia in adults living with type 1 diabetes mellitus (T1D). We aimed to determine, in people living with T1D, which oral carbohydrate treatments attain >50% non-severe hypoglycemia (glucose 3.0 to 3.9 mmol/L) resolution at time of first glucose re-check. Medline, Embase, Scopus, and Cochrane Central Register of Controlled Trials were searched for full-text studies of oral treatment for non-severe hypoglycemia in T1D. Two authors screened the results and extracted data. Amongst the four studies of multiple daily insulin injections or non-closed-loop insulin pumps, >50% hypoglycemia resolution at first re-check was only observed in two studies: exercise-induced hypoglycemia study with 20 grams of glucose treatment attaining 60% hypoglycemia resolution at 15 minutes; real-life patient recorded study with 0.2 grams per kilogram body weight (g/kg) or 0.3 g/kg or 15 g glucose tablet treatment attaining 61%, 71%, and 63% hypoglycemia resolution at 10 minutes, respectively. Two of the three studies of closed-loop insulin pumps achieved >50% hypoglycemia resolution at first re-check: 16 grams of glucose tablets at 20 minutes attained 58% hypoglycemia resolution; 10 to 30 g of sucrose attained 79 to 100% hypoglycemia resolution at 15 minutes. The optimal quantity of oral carbohydrate treatments for T1D required to attain hypoglycemia resolution at first glucose re-check varies based on cause of hypoglycemia and type of insulin management.

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Keywords: type 1 diabetes mellitus, hypoglycemia treatment, oral carbohydrates, hypoglycemia resolution

Introduction

Hypoglycemia is a common side effect of insulin pharmacotherapy for people living with type 1 diabetes mellitus (T1D).¹ Non-severe hypoglycemia is generally defined as when people living with T1D can self-treat to attain hypoglycemia resolution.²⁻⁴ Although there lacks a strict cut-off for the glucose level, glucose between 3.0 to 3.8 or 3.9 mmol/L is a common range used for the definition of non-severe hypoglycemia.¹⁻⁴

Worldwide, the widely recommended treatment for non-severe hypoglycemia is 15 grams (g) of simple carbohydrates, with first glucose re-check 15 minutes post-treatment.¹⁻⁴ This recommendation was broadly accepted into clinical guidelines decades ago and has been entrenched in diabetes care. However, this recommendation was based on expert opinion, and stems from two small-sized studies of intravenous insulin-induced hypoglycemia in people living with

T1D.^{2–6} Notably, the design of those two studies were very different from current T1D management.^{5,6} Moreover, the real-life causes of hypoglycemia are diverse, including excess insulin, delayed meals, or increased physical activity.^{1–4} People living with T1D may have preferences for hypoglycemia treatment depending on the trigger, which may include a lower insulin dose, avoiding meal delays, or avoiding unplanned physical activity.^{1–4} Furthermore, people with T1D treated with closed-loop insulin pumps where the rate of insulin delivery is decreased with the anticipation or detection of low glucose, may not need the same intensity of hypoglycemia treatment as those who are taking basal-bolus injection insulin therapy.^{7,8} Feedback from people living with T1D showed that because hypoglycemia is extremely uncomfortable and creates fear, many people will treat with more than 15 g of carbohydrates.^{7–13} Understandably, people experiencing hypoglycemia would like resolution as soon as possible.

Therefore, it is rather unlikely for the “15 grams/15 minutes” treatment to be optimal for all hypoglycemia causes and various T1D management regimens. The objective of this systematic review was to examine in adults living with T1D (population), which oral carbohydrate treatments (intervention) were able to attain >50% resolution of non-severe hypoglycemia events at first glucose recheck (outcome). For studies to be included, no comparator was required.

Materials and Methods

The inclusion criteria were the following:

- Population: adults (age ≥ 18 years) living with T1D who are able to self-treat their non-severe hypoglycemia.
- Intervention: oral simple carbohydrate treatment of defined type (such as juice or glucose tablets) and quantity (grams).
- Comparator: a comparator was not required for the study to be included. A comparator could have been a different type or quantity of oral simple carbohydrate treatment for hypoglycemia.
- Outcome: greater than 50% of hypoglycemia events resolved at first glucose re-check is the main outcome. The percentage of hypoglycemia resolution will be extracted as long as there is a pre-defined time in minutes for the first glucose re-check. The threshold glucose above which hypoglycemia is resolved can vary between studies as long as they clearly define this in their methods.

The exclusion criteria were:

- Articles that did not contain a treatment for hypoglycemia event.
- Participant age < 18 years because the pediatric population living with type 1 diabetes encompasses such a wide range of childhood developmental stages where parents and caregivers may be involved in the non-severe hypoglycemia treatment. If there was a mix of participant ages, the study was excluded if less than 50% of the participants were age 18 years or above. Whenever possible, we extracted only the data for this group if it was presented separately.
- Any non-oral form of administration for hypoglycemia treatment, for example, glucagon, intravenous dextrose.

Literature Search

Ovid MEDLINE, Embase, Scopus, and Cochrane Central Register of Controlled Trials were searched comprehensively, from 1 January 1990 to 24 March 2025. Medical Subject Headings and free-text terms that were related to diabetes, hypoglycemia, and carbohydrates were included in the search strategies, which are attached as a [Supplementary File](#).

To improve specificity, terms such as “diabetes” and “hypoglycemia” were restricted to titles, but also searched in abstracts using the adjacent “ADJ” operator to capture relevant proximity. The search was refined for studies that reported glucose outcome measures. Full-text articles published in English or French were included.

Selection Process

Two authors independently screened the literature search results and extracted the data.

Two authors also performed reference list checking. If there were disagreements, the details were discussed and perspectives were analysed until consensus was reached. If required, a third author was available for additional discussion to reach consensus.

Data Extraction

We extracted the following data from each included study: first author, year of publication, country where the study took place, number of hypoglycemia events studied, cause that induced the hypoglycemia, initial glucose level for hypoglycemia onset, type and quantity of simple carbohydrate as treatment, time of first glucose re-check, hypoglycemia threshold above which resolution is attained, percentage of hypoglycemia event resolution at time of first glucose re-check, if rebound hypoglycemia was assessed and its definition and occurrence.

Study Risk of Bias Assessment

The Newcastle-Ottawa scale for non-randomized studies was used to evaluate the risk of bias.¹⁴ The Revised Cochrane risk-of-bias tool for randomized trials “RoB 2” tool was used where applicable.

Effect Measures

The effect measure was the attainment of >50% hypoglycemia event resolution at time of first glucose re-check, which was a defined number of minutes since completion of the first oral simple carbohydrate treatment. The rationale is because people experiencing hypoglycemia feel unwell and would prefer hypoglycemia resolution as soon as possible. The ideal treatment would attain hypoglycemia resolution at first glucose recheck to minimize hypoglycemia symptoms, and avoid the need for excessive calories and prolongation of symptoms necessitating a repeat treatment.

Data Synthesis Methods

We synthesized data for studies that had both the same type and grams of simple carbohydrates orally ingested, and the same time to first glucose recheck. Synthesized data can then be used to calculate the aggregated percentage of hypoglycemia resolution at first glucose re-check for the type and quantity of oral simple carbohydrate treatment.

In addition, studies based on T1D using closed-loop insulin pumps will be reported separately from studies where these special pumps were not used. Closed-loop insulin pumps allow an added layer of hypoglycemia treatment with their abilities to decrease the insulin infusion when hypoglycemia is anticipated or detected.

We will present synthesized data in the results. A meta-analysis was not planned because we did not expect studies to often have the same type and quantity of oral simple carbohydrate treatment and the same time to first glucose re-check. Hence, we did not anticipate to have enough studies to allow for a meta-analysis.

Reporting Bias Assessment and Certainty Assessment

Hypoglycemia definition for occurrence and resolution are based on each study’s pre-defined glucose levels, and therefore there is minimal risk of bias in its assessment. Furthermore, the oral carbohydrate treatment for hypoglycemia is also defined in each study with respect to type of simple carbohydrate and time in minutes to first glucose re-check. Therefore, the intervention and outcome pose a high degree of certainty for each study’s results reporting.

Results

Study Selection

The information science specialist co-author performed the literature search. The results and screening process flow chart, according to The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols^{15,16} is presented in Figure 1.

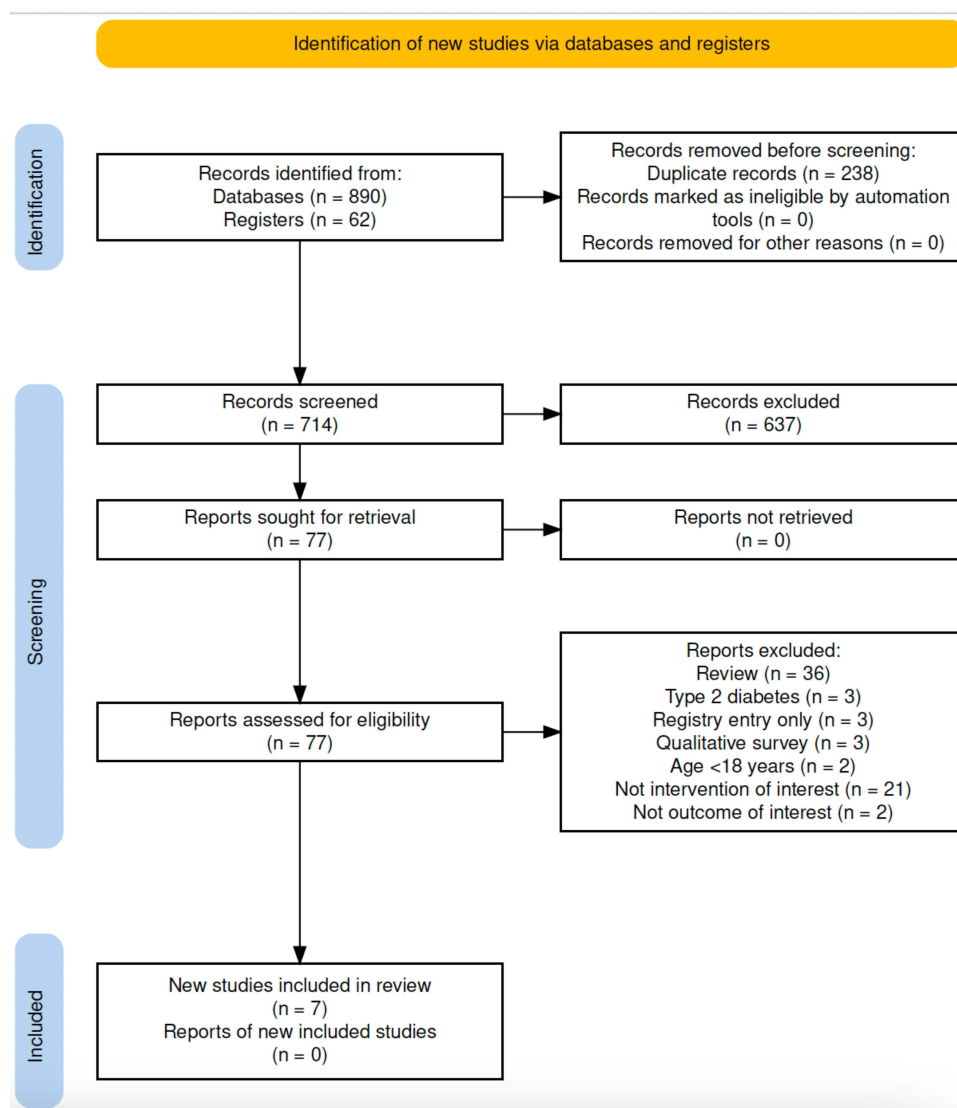


Figure 1 Flow diagram of literature search results and screening.^{15,16}

Study Characteristics

Seven studies were included, of which four were in T1D with insulin treatment via multiple daily injection insulin or insulin pump without closed-loop set-up, and their data are in [Table 1](#). The other three included studies were in T1D on a closed-loop insulin pump system, and their data are in [Table 2](#).

Four T1D Studies with Insulin Treatment (Not Using Closed-Loop Insulin Pump System)

For the four studies^{17–20} without closed-loop insulin pump use, two studies^{17,19} had >50% hypoglycemia resolution at first glucose re-check. These two studies shared hypoglycemia induction triggers that are likely much more frequent in daily life.^{17,19}

The hypoglycemia events were induced via exercise in one study (Broz et al 2021)¹⁷ where participants were monitored to exercise on an ergometer set to each participant's target heart rate that they defined as "50% of the individual heart rate reserve". When plasma glucose reached ≤ 3.5 mmol/L with symptoms, or < 3.0 mmol/L with or without symptoms, the treatment of 20 grams of glucose dissolved in 150 mL water was administered.¹⁷ The study

Table 1 Data Extracted From 4 Included Studies with Insulin Treatment (Not Using Closed-Loop Insulin Pump System)

Study 1 st author, year (country)	Hypoglycemia Events	Hypoglycemia Induction	Initial Hypoglycemia Measured Method and Mean ($\pm$ SD; mmol/L)	Simple Carbohydrate Type(s) and Grams (g)	Time of 1 st glucose re-check (minutes)	Glucose (mmol/L) above which Hypoglycemia is Resolved	Percent Hypoglycemia event Resolution at 1 st Glucose re-check	Rebound Hyperglycemia Part of Study Design
Broz 2021 (Czech Republic) ¹⁷	5	Exercise	Plasma glucose 2.8 (0.4)	Glucose 20g in 150 mL water	15	3.9	60	Yes; no rebound hyperglycemia (glucose >10 mmol/L) within 60 mins post simple carbohydrate treatment
Cheng 2024 (Canada) ¹⁸	29	Rapid insulin analog subcutaneous bolus	Plasma glucose 3.6 (0.3)	Dex4 glucose tablets 16g	20	4.0	31	Yes; 1 event had rebound hyperglycemia (glucose >10 mmol/L at 60 minutes post initial simple carbohydrate treatment
McTavish 2015 (New Zealand) ¹⁹	132	Real-life triggers – data from data recorded by each participant	Capillary glucose 3.2 (0.5)	Dextro glucose tablets 0.2 g/kg body weight	10	4.0	61	Yes; defined as capillary glucose >8 mmol/L at 10 mins post simple carbohydrate treatment. Occurred in 2 events treated with 0.3g/kg body weight; 1 event treated with 15g.
	141		3.2 (0.6)	0.3 g/kg body weight			71	
	136		3.1 (0.6)	15g			63	
Taleb 2023 #1 (Canada) ²⁰	32	Rapid insulin analog subcutaneous bolus	Plasma glucose 3.1 (0.4)	Dex4 tablets 16g	15	4.0	19	Yes; 0 events treated with 16g carbohydrates; 6 events treated with 32g carbohydrates had rebound hyperglycemia (glucose >10 mmol/L within 60 minutes post initial treatment.
	32		3.2 (0.3)	Dex4 tablets 32g			47	
	29		2.7 (0.2)	Dex4 tablets 16g			21	
	29		2.6 (0.3)	Dex4 tablets 32g			24	

Table 2 Data Extracted From 3 Included Studies with Closed-Loop Insulin Pumps

Study 1 st author, year (country)	Hypoglycemia Events	Hypoglycemia Induction	Initial Hypoglycemia Measured Method and Mean ($\pm$ SD; mmol/L)	Simple Carbohydrate Type(s) and Grams (g)	Time of 1 st Glucose re- check (minutes)	Glucose (mmol/L) above which Hypoglycemia is Resolved	Percent Hypoglycemia Event Resolution at 1 st Glucose re-check	Rebound Hyperglycemia Part of Study Design
Gingras 2018 *47 adults; 10 adolescents (Canada)²¹	48	Secondary analysis of insulin pump with closed-loop delivery studies supervised at research clinic	Plasma glucose 3.1 (0.4)	Dex4 glucose tablets 16g	15	4.0	38 (15 mins post 1 st treatment) 58 (20 mins post 1 st treatment) 69 (30 mins post 1 st treatment)	Yes; no rebound hyperglycemia (glucose >10 mmol/L) at 60 mins post simple carbohydrate treatment
Grassi 2021 (Chile)²²	33	Real-life triggers – data from data recorded by each participant. Insulin pump with predictive low glucose suspension if predicted glucose <3.3 mmol/L in the next 30 mins	Capillary blood glucose 3.0 (0.4)	Sucrose dissolved in 100 mL water; 10g if CBG >2.8 mmol/L 20g if CBG <=2.8 mmol/L	15	3.9	79	Yes; no rebound hyperglycemia (glucose >13.9 mmol/L) at 30 minutes post simple carbohydrate treatment
	26		3.2 (0.5)	15g if CBG >2.8 mmol/L 30g if CBG <=2.8 mmol/L			100	
Taleb 2023 #2 (Canada)²³	40	Secondary analysis of insulin pump with closed-loop delivery studies supervised at research clinic	Plasma glucose 3.1 (0.6)	Oral liquid carbohydrate 15g or Dex4 tablets 16g	15	4.0	45	Yes; no rebound hyperglycemia (glucose >10 mmol/L) at 60 mins post simple carbohydrate treatment

Notes: *Gingras et al 2018 study²¹ included 47 adults and 10 adolescents – the results were reported together without separability between the adults and adolescents.

reported the increase in plasma glucose at 15 minutes after this first treatment. Although the authors did not define the glucose threshold for hypoglycemia resolution, the presented results allowed for calculation of the glucose at time of first re-check. Because the current common threshold for hypoglycemia resolution is set at 3.9 mmol/L, we applied this threshold in the data synthesis to show the 60% hypoglycemia resolution at first glucose re-check.

The McTavish et al 2015 study¹⁹ was designed for people living with T1D to take home the oral hypoglycemia treatments and take them in the order based on sealed envelopes. Whenever a study participant had onset of hypoglycemia due to any type of real-life trigger, the participant opened a sealed envelope and proceeded to treat based on one of the three treatments listed inside the envelope. Notably, for the 0.2 g of glucose tablets per kilogram of body weight (g/kg), the range of glucose tablets was 10.5 to 19.5 g. For their 0.3 g of glucose tablets per kilogram of body weight, the range of glucose tablets was 15 to 30 g. Despite the substantial overlap between the three treatments in this study,¹⁹ the results were presented for the participants based on their assigned oral carbohydrate treatment (0.2g/kg or 0.3g/kg or 15g). In particular, the overlap in the actual quantities of glucose used for treatment in the 0.2 g/kg and the 15 g groups showed very similar percentages of hypoglycemia resolution at 10 minutes: 61% and 63%, respectively. Their 0.3 g/kg treatment only increased the hypoglycemia resolution by an extra 10% at 10 minutes, when compared to their 0.2 g/kg treatment.

The two studies^{18,20} that attained less than 50% hypoglycemia resolution at first glucose re-check were by the same research group that induced hypoglycemia with a subcutaneous bolus dose of rapid-acting insulin that was standardized based on both the participant's weight and baseline glucose level at the start of their study protocol. The Taleb et al 2023 study²⁰ intended to study mild hypoglycemia 3.0 to 3.5 mmol/L, and moderate hypoglycemia <3.0 mmol/L. However, this intent was difficult to achieve with the mild hypoglycemia group reaching into the <3.0 mmol/L range. Nevertheless, 32 g of glucose tablets in participants with hypoglycemia (mean 3.2, standard deviation (SD) 0.3 mmol/L) attained 47% hypoglycemia resolution at 15-minute re-check. The Cheng et al 2024 study¹⁸ achieved mild hypoglycemia more often in the group that had mean plasma glucose 3.6 SD 0.3 mmol/L, where 16 g of glucose tablets attained 31% hypoglycemia resolution by the 20-minute re-check.

All four of these studies^{17–20} included an assessment for rebound hyperglycemia.^{24,25} Three studies shared the same definition for rebound hyperglycemia to be glucose >10 mmol/L at 60 minutes post-oral carbohydrate treatment.^{17,18,20} The rebound hyperglycemia in these three studies^{17,18,20} was minor, with the highest being near 10% amongst participants treated with 32 g of glucose tablets. McTavish et al 2015 study's definition for rebound hyperglycemia was notably much stricter, being glucose >8 mmol/L at 10 minutes post-oral carbohydrate treatment.¹⁹

Three of the Included Studies Used a Closed-Loop Insulin Pump System

Closed-loop insulin pump systems are designed for feedback from the detected or anticipated glucose levels to cause an adjustment in the insulin pump's delivery rate.^{21–23} If low glucose or anticipated low glucose is detected, then the automated insulin delivery programming can decrease the insulin delivery rate or temporarily suspend insulin delivery. Therefore, the use of a closed-loop insulin pump system adds a layer of protection or assisted treatment of hypoglycemia.

Two included studies are secondary analyses of closed-loop insulin delivery systems being used in a setting supervised by the study teams.^{21,23} These two studies reached similar levels of hypoglycemia, and treatment with 15 to 16 g of simple carbohydrates showed a 38 to 45% resolution if the first glucose re-check was at 15 minutes.^{21,23} Notably, there was an ongoing rise in plasma glucose in the Gingras et al 2018 study,²¹ which detected that the resolution increased from 38% at 15 minutes, to 58% at 20 minutes, and 69% at 30 minutes.

Grassi et al 2021 designed their study²² to aim for data analyses based on mild hypoglycemia that they defined as glucose 2.9 to 3.8 mmol/L, and moderate hypoglycemia that they defined as glucose 2.8 mmol/L or less. They doubled the quantity of sucrose treatment for glucose $\leq$ 2.8 mmol/L. This increased quantity of treatment for glucose $\leq$ 2.8 mmol/L could have contributed to their higher percentage of hypoglycemia resolution.

All three studies^{21–23} assessed for rebound hyperglycemia which was not a concern. Two studies defined rebound hyperglycemia as glucose >10 mmol/L at 60 minutes post-treatment, and one study defined it as glucose >13.9 mmol/L at 30 minutes post-treatment.

Risk of Bias Assessment

The assessment of the risk of bias was based on the Newcastle-Ottawa scale¹⁴ ratings presented in Table 3 and Table 4. There was a low risk of bias for all the included studies. All studies were ultimately categorized as non-randomized for the purpose of this systematic review question because all study results were analysed according to the type and quantity

Table 3 Newcastle-Ottawa Risk of Bias Assessment for 4 Included Studies

First Author Publication Year (Country)	Broz 2021 (Czech Republic) ¹⁷	Cheng 2024 (Canada) ¹⁸	McTavish 2015 (New Zealand) ¹⁹	Taleb 2023 #1 (Canada) ²⁰
Selection				
Representativeness of exposed cohort	Yes	Yes	Yes	Yes
Selection of non-exposed cohort	Not applicable			
Ascertainment of exposure (hypoglycemia treatment)	Yes	Yes	Yes	Yes
Outcome of interest (hypoglycemia resolution) was not present at start of study	Yes	Yes	Yes	Yes
Comparability				
Study controls for grams of simple carbohydrate administered	Yes	Yes	Yes*	Yes
Study controls for time to hypoglycemia resolution	Yes	Yes	Yes*	Yes
Outcome				
Assessment of outcome	Yes	Yes	Yes*	Yes
Follow-up long enough for outcome	Yes	Yes	Yes	Yes
Adequacy of follow-up	Yes	Yes	Yes	Yes

Notes: *McTavish et al 2015 study¹⁹ – participants carried out the glucose measurements and oral carbohydrate treatment by themselves, and recorded their results for the study team to analyse.

Table 4 Newcastle-Ottawa Risk of Bias Assessment for 3 Closed-Loop Insulin Pump Studies

First author Publication Year (Country)	Gingras 2018 *47 adults; 10 Adolescents (Canada) ²¹	Grassi 2021 (Chile) ²²	Taleb 2023 #2 (Canada) ²³
Selection			
Representativeness of exposed cohort	Yes*	Yes	Yes
Selection of non-exposed cohort	Not applicable		
Ascertainment of exposure (hypoglycemia treatment)	Yes	Yes	Yes
Outcome of interest (hypoglycemia resolution) was not present at start of study	Yes	Yes	Yes
Comparability			
Study controls for grams of simple carbohydrate administered	Yes	Yes**	Yes
Study controls for time to hypoglycemia resolution	Yes	Yes**	Yes
Outcome			
Assessment of outcome	Yes	Yes**	Yes
Follow-up long enough for outcome	Yes	Yes	Yes
Adequacy of follow-up	Yes	Yes	Yes

Notes: *Gingras et al 2018 study²¹ included 47 adults and 10 adolescents – the results were reported together without separability between the adults and adolescents.
**Grassi et al 2021 study²² was designed for participants to detect and treat their hypoglycemia events at home as instructed by the study team.

of carbohydrate treatments received. The order of receiving hypoglycemia treatment type did not influence the data collection or analysis process. The type and quantity of hypoglycemia treatment was documented and analysed with others that also received the same treatment. Each hypoglycemia event was treated independently of previous or subsequent hypoglycemia events.

Results of Syntheses, Reporting Biases, and Certainty of Evidence

Data syntheses were very limited because of the differences in study protocols, including study participants' characteristics, insulin treatment format, type and quantity of simple carbohydrate treatment, and time to first glucose re-check.

Only two studies of closed-loop insulin pumps by the same study group met the criteria for data synthesis.^{21,23} The only data synthesis possible has already been presented in the results where the percentage resolution with 15 to 16 g of simple carbohydrates produces a 38 to 45% resolution at 15-minute re-check.

For the question raised in this systematic review, reporting biases are less applicable. This is because hypoglycemia detection and resolution are based on glucose measurements. Hypoglycemia oral carbohydrate treatment types and quantities are also clearly reported in all studies. Based on these features, the certainty of evidence in these studies is also high.

Discussion

Studies on non-severe hypoglycemia treatment in people living with T1D are very heterogenous in their design both in the quantities of simple carbohydrate used and the first glucose re-check time. Hypoglycemia events are stressful and uncomfortable situations and people can develop fear of hypoglycemia.^{10,13} Lack of timely resolution of hypoglycemia is an important concern for people living with T1D, both for their own wellbeing and for the safety of others in their surroundings who may be affected by somebody experiencing hypoglycemia. Therefore, recommendations for hypoglycemia treatment would benefit from having at least 50% resolution at first recheck time to minimize the time spent in low glucose.

For T1D not treated with closed-loop insulin pump systems and hypoglycemia not caused by a subcutaneous bolus of excess rapid-acting insulin, treatment with 0.2 g/kg or 0.3 g/kg or 15g or 20 g of simple carbohydrates and first glucose re-check at 10 or 15 minutes is associated with 60 to 71% resolution.^{17,19} Hypoglycemia caused by receiving a subcutaneous bolus of excess rapid-acting insulin often requires more than 32 grams of carbohydrates for treatment,^{18,20} and more studies are needed for the actual quantity to recommend. For T1D treated with closed-loop insulin pump systems, treatment with 10 to 15 g of sucrose dissolved in water is associated with 79 to 100% resolution at 15-minute re-check if the initial non-severe hypoglycemia was >2.8 mmol/L.²²

Rebound hyperglycemia was quite infrequent in the studies. The most common definition for rebound hyperglycemia was glucose >10 mmol/L at 60 minutes post-treatment. We recommend for this to be adopted as the definition for rebound hyperglycemia to unify future studies in this field. This fits well with the current continuous glucose monitors' time-in-range's upper limit being 10 mmol/L. Using machine learning to predict rebound hyperglycemia versus the dawn phenomenon could be a promising near-future implementation. As demonstrated by Montaser and Shah,²⁶ employing continuous glucose monitoring and machine learning can help identify at-risk individuals for early intervention, potentially improving outcomes and delaying the progression of diabetic retinopathy.

The Cheng et al 2024 study¹⁸ design presents a new strategy for hypoglycemia treatment by showing that the time spent in hypoglycemia (<3.9 mmol/L) was significantly decreased when treatment was initiated at plasma glucose <4.5 mmol/L or <5.0 mmol/L rather than <3.9 mmol/L. Moreover, there was no significant increase in rebound hyperglycemia. This is an important element that could be integrated into future hypoglycemia treatment studies.

We highlight as well that all seven studies were in the outpatient setting, and none were performed on patients admitted to the hospital. Hypoglycemia in hospitalized patients presents additional challenges because the patient is no longer in their familiar surroundings where they were capable of and had easy access to simple carbohydrates for hypoglycemia treatment.^{2,27}

Limitations of this systematic review include that we focused on defining hypoglycemia resolution as attainment of a defined glucose threshold at a defined re-check time. We acknowledge that hypoglycemia symptoms may have resolved before or after the attainment of glucose threshold resolution, and this could not be accounted for in the studies based on their design and reported data. Future studies could incorporate patient-oriented outcomes where people living with T1D would report whether their hypoglycemia symptoms were or were not resolved at the timed glucose recheck. This would

lead to a more comprehensive definition of hypoglycemia resolution: glucose recheck ≥ 4.0 mmol/L and hypoglycemic symptoms gone. We gave equal weight to studies where participants were monitored by the study team, and studies where patient carried out the study protocol at home. However, at home, participants may have had access to other sources of carbohydrates that they could have possibly and unintentionally not recorded for the study team. Also, we searched for full text articles in English and French due to the language proficiencies of the authors. Thus, we would have missed studies in other languages or abstracts that were not subsequently published as articles, which could have biased this review.

Implications of Review Findings

The widely recommended 15 grams of simple carbohydrates with first glucose re-check in 15 minutes is based on weak evidence for people living with T1D. Notably, when an excess bolus of rapid-acting insulin causes a more severe hypoglycemia (where many participants' glucose dipped below 3.0 mmol/L), even 32 g of glucose tablets only has a very low percentage of resolution at 15 minutes post-treatment.²⁰ On the other hand, closed-loop insulin delivery systems offer an additional layer of treatment for hypoglycemia by decreasing the insulin delivery, and therefore a much higher percentage resolution can be attained. We suggest for hypoglycemia recommendations to incorporate a wider range of carbohydrate quantities required for treatment.

Conclusions

The optimal quantity of oral carbohydrate treatments for T1D required to attain hypoglycemia resolution at first glucose re-check varies based on cause of hypoglycemia and type of insulin management. Higher rates of hypoglycemia resolution are achieved in those who use closed-loop insulin pumps where insulin delivery rate is decreased when lower glucose levels are detected or predicted. Future studies on non-severe hypoglycemia treatment are recommended to try to catch and intervene when the glucose is 3.0 mmol/L or above, so that more severe hypoglycemia requiring more oral carbohydrates are not contributing to decreasing the studies' resolution rates.

Abbreviations

g, grams; g/kg, grams per kilogram body weight; SD, standard deviation; T1D, type 1 diabetes.

Data Sharing Statement

No new data was generated in this article.

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Author Contributions

Nicole Prince: methodology, investigation, formal analysis, validation, writing – review and editing. Heather Lochnan: formal analysis, writing – review and editing. Risa Shorr: methodology, writing – review and editing. Annie Garon-Mailer: formal analysis, writing – review and editing. Cathy J. Sun: conceptualization, methodology, investigation, formal analysis, validation, visualization, supervision, writing – original draft, writing – review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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