Review Article

Clinical relevance of short-term glycemic variability in children and adolescents with type 1 diabetes: a narrative review

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Background and Objective: In recent years, there has been growing interest in glycemic variability within the scientific community, particularly regarding its potential as an independent risk factor for diabetes-related long-term complications. This narrative review aimed to provide a comprehensive overview of short-term glycemic variability in children and adolescents with type 1 diabetes (T1D).

Methods: We performed a search of published literature on the PubMed MEDLINE database using the following combination of search terms: "glycemic variability", "pediatric", "type 1 diabetes", and "children".

Key Content and Findings: The widespread use of continuous glucose monitoring (CGM) systems has facilitated the characterization and quantification of glycemic fluctuations. Over the years, several metrics for assessing glycemic variability have been developed. Children and adolescents with T1D often experience wide and frequent glycemic excursions due to behavioral and hormonal factors. Several studies suggest a potential link between glycemic variability and an increased risk of diabetes-related complications.

Conclusions: Glycemic variability has become an integral aspect of the routine clinical management of youths with T1D, serving as a valuable therapeutic target. However, achieving recommended glycemic targets in this population remains challenging. Further long-term data are needed to definitively establish the role of glycemic variability in the development of complications.

Keywords: Complications; continuous glucose monitoring (CGM); insulin; pediatrics; time in range (TIR)

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Introduction

Background

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the destruction of pancreatic β-cells, leading to insulin deficiency and requiring lifelong insulin substitutive therapy (1). It affects millions of individuals worldwide, with a substantial portion being diagnosed during childhood and adolescence (2).

Managing T1D in youth poses unique challenges, primarily related to the developmental, emotional, and physiological changes that characterize growth and maturation. The primary objective of T1D management in pediatric age is to prevent associated morbidity and mortality by maintaining glucose levels as close as possible to the euglycemic range (3). The preventing role of tight

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glycemic control on long-term complications has been recognized for decades, since the Diabetes Control and Complications Trial (DCCT) revealed a direct correlation between the risk of diabetes-related complications—including retinopathy, nephropathy, neuropathy, and macrovascular disease—and glycated hemoglobin A1C (HbA1c) levels (4). HbA1c, the most widely adopted marker for assessing longitudinal glucose control in individuals with diabetes, is strongly influenced by the concentration of blood glucose over the preceding 8 to 12 weeks (5). International guidelines for children and adolescents with T1D set a target HbA1c below 7% to define satisfactory glucose control (5).

The widespread adoption of continuous glucose monitoring (CGM) systems in clinical practice has provided more detailed insights into daily glucose patterns of individuals with T1D than the sole HbA1c levels. Glycemic variability can be classified as short-term, consisting of daily oscillations in blood glucose levels—including both their amplitude and frequency—and long-term, referring to variations in longitudinal glucose control markers such as HbA1c. In recent years, short-term glycemic variability has garnered increasing interest among the scientific community, particularly regarding its potential implication as an independent risk factor for long-term complications.

Rationale and knowledge gap

Understanding glycemic variability in pediatric T1D is crucial for several reasons. Firstly, children and adolescents frequently experience glucose excursions due to factors such as growth spurts, varying physical activity levels, dietary habits, and hormonal changes associated with puberty. Achieving recommended targets of glycemic variability is challenging in this population, even with the use of advanced therapeutic tools such as second-generation automated insulin delivery systems (6,7). Secondly, the impact of glycemic variability on long-term outcomes, including the development of microvascular and macrovascular complications, remains unclear and is object of ongoing research and debate (8) (*Figure 1*).

Objective

This narrative review aimed to provide a comprehensive overview of glycemic variability in pediatric individuals with T1D. By reviewing existing literature, we explored measurement methodologies, clinical factors contributing to glycemic variability in the pediatric population, and evidence regarding its association with long-term complications. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-114/rc).

Methods

We performed a comprehensive search of published literature using the PubMed MEDLINE database from January 2010 to January 2024. We used the following combination of search terms: "glycemic variability", "pediatric", "type 1 diabetes", and "children". The literature search was conducted equally by all co-authors, and any disagreements were resolved by G.S.

Non-English language papers, case reports, and editorials were excluded. Particular emphasis was placed on randomized controlled studies, observational studies, systematic reviews, and meta-analyses.

Studies involving adult populations on specific topics with scarce pediatric data, such as measurement methods and long-term complications, were also considered. The search strategy is summarized in *Table 1*. A total of 71 papers (4 literature reviews, 3 guidelines, 10 randomized controlled trials, and 54 observational studies) were included in the review.

Glycemic variability assessment

In recent years, CGM systems have emerged as the standard for monitoring children and adolescents with T1D (5). These wearable devices offer real-time measurements of interstitial glucose levels, providing valuable insights into average daily glucose trends and time spent within, above, and below the target glycemic range, allowing the prompt identification of the duration and extent of hypo- and hyperglycemia.

Furthermore, CGM facilitate accurate retrospective analysis of daily glucose fluctuations, offering insights into the amplitude of sensor glucose peaks and valleys and their frequency. However, quantifying glucose variability remains challenging due to the asymmetry of the blood glucose measurement scale, where the hypoglycemic range is significantly narrower than the hyperglycemic range, rendering excursions in glucose levels within the hypoglycemic range clinically more significant (9).

Moreover, obtaining a reliable estimate of glucose

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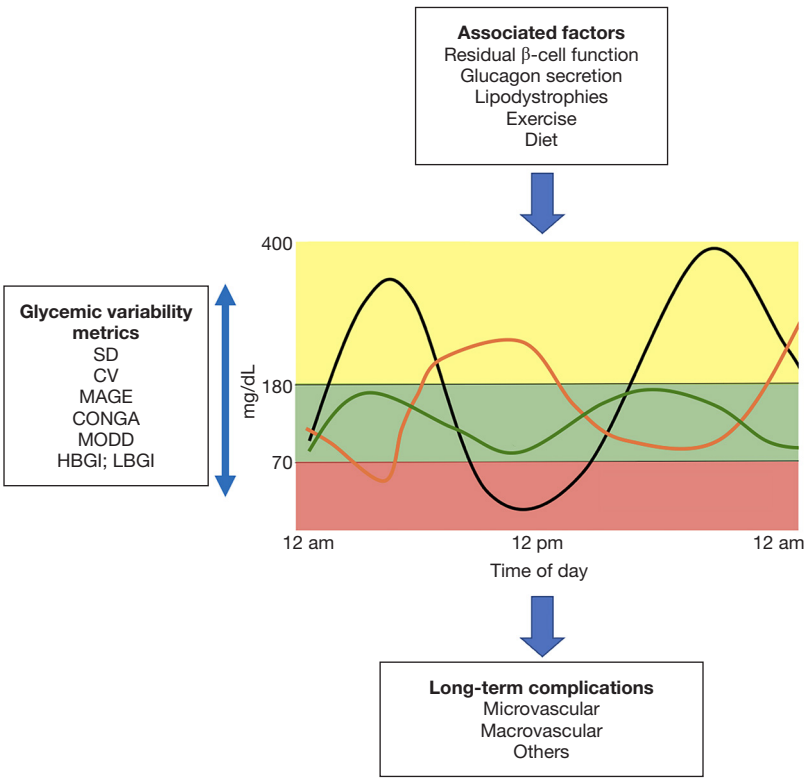

Figure 1 Graphical summary of assessment, associated factors, and long-term outcomes of glycemic variability in pediatric type 1 diabetes. The black, red, and green lines represent different patterns of glycemic variability over a 24-hour period. Specifically, the black line expresses a wide excursion of glucose levels, the red line indicates a moderate glucose variability, and the green line reflects a flat glucose profile. SD, standard deviation; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; CONGA, continuous overlapping net glycemic action; MODD, mean of daily differences; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index.

Table 1 The search strategy summary

Items	Specification
Date of search	31 January 2024
Databases and other sources searched	PubMed MEDLINE
Search terms used	"Glycemic variability", "Pediatric", "Type 1 diabetes", "Children"
Timeframe	January 2010–January 2024
Inclusion and exclusion criteria	Inclusion: meta-analyses, systematic reviews, randomized controlled studies, and observational studies
	Exclusion: non-English language papers, case reports, editorials
Selection process	All authors worked independently on the selection of papers. Disagreements between authors were resolved by discussion and consensus

variability necessitates CGM data over a sufficient time window. An analysis of CGM data from children and adolescents with T1D suggested a minimum interval of twelve days for assessing glucose variability, with no more than four hours between each glucose measurement (10). Conversely, Piona *et al.* found that a 4-week dataset better

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Table 2 Summary of glycemic variability metrics

Metric	Description	Advantages	Disadvantages
SD	Variation of sensor glucose	Easily calculated	Typical non-normal distribution of blood glucose values
CV	SD/mean glucose ×100	Easily calculated; reliable predictor of hypoglycemia risk; correlation with TIR and TITR	Disparity between within-day CV and total CV; low discriminant ratio
MAGE	Calculated from excursions of sensor glucose exceeding 1 SD	Assessment of glycemic amplitude	Lack of information about frequency; complexity of calculation
CONGA	Measurement of duration and degree of glucose fluctuations	Assessment of the frequency of glucose variations	Complexity of calculation
MODD	Mean of absolute differences between glucose values measured at the same time of day on two consecutive days	Assessment of between-day glucose variability	Lack of information about within-day variability; complexity of calculation
HBGI, LBGI	Risk indexes of hypo- and hyperglycemia, calculated on logarithmic basis	Provide useful information about hypo- and hyperglycemia risk	Overlap with other metrics
ADRR	Evaluates glycemic variability and classifies risk of hypoglycemia and hyperglycemia	Can be calculated also in individuals on self-monitoring of blood glucose	Further validation is needed in youth with type 1 diabetes

SD, standard deviation; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; CONGA, continuous overlapping net glycemic action; MODD, mean of daily differences; HBGI, high blood glucose index; LBGI, low blood glucose index; ADRR, average daily risk range; TIR, time in range; TITR, time in tight range.

reflects glucose variability among intermittently scanned CGM users, while a 2-week period can provide acceptable accuracy in real-time CGM users (11).

Several CGM metrics quantifying glycemic variability have been developed over the years (*Table 2*). The standard deviation (SD) of sensor glucose is the most immediate metric, easily calculated by CGM systems alongside the mean sensor glucose. This indicator has demonstrated a good capability to assess the stability of glucose control due to the positive correlation between SD and HbA1c (12). However, its main limitation lies in the non-normal distribution of blood glucose values (13).

The coefficient of variation (CV) is the most commonly adopted indicator of glycemic variability in clinical practice and experimental studies. It is calculated by dividing SD by sensor mean glucose. The international consensus for CGM data interpretation defined CV as the primary indicator of glycemic variability due to its relative sensitivity to hypoglycemia compared to SD alone, and its ease of calculation (14). CV has been identified as a significant predictor of hypoglycemia, particularly of time spent with glucose <54%, compared to other CGM metrics (15-17). Furthermore, several studies have investigated the relationship between CV and other glucose control indicators (18). A cross sectional study on 195 individuals with T1D found a strong correlation between CV and time in range (TIR) 70–180 mg/dL (19), while a pediatric study on 854 CGM users identified CV as a predictor of longer time in tight range, a novel metric assessing the time spent in narrower range between 70 and 140 mg/dL (20). A subanalysis of data from five different phase 3 trials demonstrated a significant influence of within-day CV on HbA1c and daily mean glucose (21). Conversely, some studies have revealed an absent or only partial relationship between CV and HbA1c (16,18), while Castañeda *et al.* defined CV as a poor marker of hypoglycemia risk based on data from 10,404 advanced hybrid closed-loop users (22). Based on literature data, a target of 36% has been suggested to define stable glucose control (14). However, this target refers to the within-day CV, while most CGM platforms automatically calculate the total CV of the analyzed time frame. This disparity represents a limit to the interpretation of glycemic variability in clinical practice, as evidenced by a retrospective study on 104 subjects with T1D, where 21% exhibited a substantial discrepancy between within-day and total CV (23). Moreover, the threshold of 36% might be inadequate to ensure low hypoglycemia, as indicated by data from 1,002,946 intermittently-scanned CGM readers, showing that achieving the recommended target of <1% time below 54 mg/dL corresponds to a within-day CV

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below 33.5% (24). As an additional limit, a subanalysis of the Juvenile Diabetes Research Foundation dataset revealed that CV has the lowest discriminant ratio among all glycemic variability metrics, indicating poor ability to detect individual variation within a population (25).

The mean amplitude of glycemic excursion (MAGE) focuses on the width of glycemic variations and is calculated from excursions of sensor glucose exceeding 1 SD. Generally, a 2-day interval of CGM data is sufficient to extrapolate MAGE (26). Despite being a promising marker of glucose variability, its reliability is limited by the lack of information about the time taken by glucose values to fluctuate and excursions <1 SD (27).

Additional glucose variability metrics include the continuous overlapping net glycemic action (CONGA), which accounts for the frequency of glucose levels variations, the mean of daily differences (MODD), assessing between-day glucose variability, and indexes of the risk of hypo- and hyperglycemia (e.g., High Blood Glucose Index, Low Blood Glucose Index, Glycemia Risk Index) (28,29). While useful in characterizing different patterns of glucose variations, their complexity of calculation and overlap with other metrics limit their application in clinical practice (30). Additionally, there is currently no consensus on recommended targets. Another valuable metric for evaluating glycemic variability and classifying the risk of hypoglycemic and hyperglycemic episodes is the average daily risk range (ADRR), particularly for individuals conducting self-monitoring of blood glucose with a minimum of 3 measurements per day (31).

Associated factors

Glucose homeostasis is intricately regulated by hormonal pathways involving pancreatic islets, the liver, the gut, and the nervous system. In healthy individuals, these regulators respond to physiological conditions such as fasting, food intake, and physical activity to maintain stable glucose levels (9). In individuals with T1D, this complex homeostasis is seriously compromised due to insulin deficiency. Additionally, exogenous insulin therapy may itself induce unwanted glucose fluctuations, leading to patient exposure to hypoglycemia.

The poor or absent residual β-cell function typical of individuals with T1D results in marked glycemic variability compared to other types of diabetes. For instance, when comparing CGM data between youths with T1D and those with Wolfram syndrome—a genetic syndrome causing non-autoimmune diabetes—the former consistently exhibit worse glycemic variability metrics (32). Supporting the relationship between residual β-cell function and glucose variability, a longitudinal study on 78 newly diagnosed children with T1D found increased glycemic stability among individuals undergoing partial remission phase (33). Additionally, post-hypoglycemic hyperglycemia, a pattern strongly correlated with glycemic variability, has been identified as a reliable marker of partial remission phase (34).

However, β-cell secretion may not be the sole process involved in the disruption of glucose homeostasis for people with T1D. According to a secondary analysis on 28 participants of the Diabetes Research in Children Network study, impaired glucagon secretion in response to insulin-induced hypoglycemia may be associated to worse CV and CONGA values (35).

Glycemic variability can be also correlated to the concomitant presence of T1D and metabolic syndrome. This association, which has become unfortunately common due to the increasing trend of obesity in Western countries, adds the mechanism of insulin resistance to the already compromised glucose homeostasis in T1D. Notably, a multicenter cross-sectional study involving 207 adults showed higher CV levels in subjects with T1D associated to metabolic syndrome (36). However, adiposity seems to be positively associated with time spent in hyperglycemia but not with glycemic variability metrics in youths with T1D (37).

Skin issues related to diabetes management may hinder the achievement of satisfactory glucose control (38). Insulin-induced lipodystrophies are the most common dermatological complications in individuals with T1D. By altering the regular absorption of insulin in the subcutaneous tissue, these skin lesions have been identified as potential determinants of glycemic excursions (39). A correlation between the presence of lipodystrophy and higher CV and SD of sensor glucose was detected in a cohort of 212 children and adolescents with T1D (40). Similarly, Gupta *et al.* reported higher MAGE and CONGA among subjects injecting insulin at lipohypertrophy sites (41).

Younger children with T1D are well-known to experience high rates of glycemic excursions. Achieving recommended targets of CV and other glucose control indicators in this age group remains challenging, likely due to dietary habits and underlying hormonal factors affecting insulin sensitivity. To support this theory, an analysis of 4-week CGM data of 107 youths with T1D showed that pre-pubertal children have higher values of glucose SD and CV compared to pubertal and post-pubertal (42).

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Physical activity is widely acknowledged as one of the main reasons for glycemic fluctuations in people with T1D, with the type and duration of exercise responsible for distinct glucose patterns. Aerobic activity, defined as prolonged exercise with low-to-moderate intensity, is associated with an increased risk of hypoglycemia (43). Conversely, anaerobic high-intensity exercise can be associated with acute hyperglycemia (44). Studies combining CGM and accelerometry data found that physical activity leads to a higher risk of nocturnal hypoglycemia, with an increase of 60–80% every 60 minutes of activity (45,46). Additionally, there was a 31% increased risk of hypoglycemia among adolescents with more than 30 minutes of moderate-to-vigorous physical activity (46). In contrast to this evidence, a real-world analysis on ten adolescents with T1D practicing their usual physical activity over a 14-day period, showed an inverse correlation between the total amount of moderate and vigorous physical activity and overall glucose variability metrics, including CV and SD (47), while Rebesco *et al.* did not detect any difference in CV, SD, and MAGE between physically active and sedentary days (48). Similar results emerged from a cohort of preschoolers, where moderate-to-vigorous physical activity appeared to negatively affect parental fear of hypoglycemia, without any significant correlation with glycemic variability (49). These data suggest an overall benefit of regular exercise on glycemic stability, with the advantages of a good level of fitness exceeding the disadvantages of the risk of hypo- and hyperglycemia during and after exercise. In support of this hypothesis, a study on nineteen adolescents with T1D revealed an inverse association between the level of aerobic fitness, measured by maximal aerobic capacity (VO_2max), and MAGE (50).

Among lifestyle habits, even sleep characteristics seem to influence the daily glucose level variability. A cross-sectional study on 84 children with T1D found that poor sleep efficiency, longer sleep onset latency, and nocturnal wake duration are significantly correlated with higher overnight glycemic variability (51).

Nutrition plays a fundamental role in the management of T1D, with healthy and balanced diets being crucial for achieving optimal glucose control. It is well-established that the quality and the balance of macronutrients have a substantial impact on postprandial glycemic control and overall glucose variability. In a real-world study on 208 youth with T1D taking pictures of each meal over a 10-day observation period to allow an accurate evaluation of macronutrient composition, a higher glycemic variability assessed by CV and glucose SD was observed following meals with more carbohydrates in comparison to fat- and protein-based meals (52). Similar results were obtained from a cohort of preschoolers, with greater postprandial glucose variability recorded after meals with high carbohydrate content (53). Nevertheless, fats and proteins are also known to have an effect on postprandial glycemic variability, manifesting as late hyperglycemia 3–6 hours after the meal (54,55). Alongside the overall macronutrient intake, an accurate carbohydrate counting is crucial to improve glycemic control, especially among users of automated insulin delivery systems. Brazeau *et al.* demonstrated that inaccurate carbohydrate counting is a predictor of higher glycemic variability measured by MAGE and SD (56).

Gluten-free foods, known to have high glycemic index and low-fiber content, can exacerbate glycemic excursions in subjects with concomitant T1D and celiac disease. In support of this hypothesis, a pediatric case-control study found that gluten-free diet is associated with greater glycemic excursions in youths with T1D and celiac disease (57). Conversely, Mozzillo *et al.* reported similar glucose metrics between children with T1D and celiac disease and those with T1D only, except for individuals who were not strictly adhering to a gluten-free diet, who presented higher hyperglycemia levels (58).

Glycemic variability and long-term outcomes

In addition to the established relationship between glycemic variability and the risk of acute complications of diabetes, such as severe hypoglycemia (59), the role of glucose excursions as independent risk factor for long-term complications has garnered significant interest among researchers in recent years.

Long-term complications of T1D consist of microvascular damage, including retinopathy, neuropathy, and nephropathy, as well as macrovascular diseases. These complications usually develop insidiously, and clinical signs may occur several years after the onset of vascular damage (60). Hence, regular screening procedures and tailored therapeutic interventions aimed at achieving tight glycemic control become imperative, especially during pediatric age.

Since the DCCT and the Epidemiology of Diabetes and Interventions and Complications (EDIC) study (4,61), HbA1c has been recognized as a predictor of long-term complications and has been considered the gold standard for assessing glycemic control (5). However, subsequent data have suggested that HbA1c and average glucose levels

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may not be the sole determinants of diabetes-related long-term complications (62).

In recent years, the relationship between glycemic variability and the occurrence of complications has been widely investigated, with controversial findings. In a systematic review of the literature, the role of glycemic variability emerged as irrelevant for the development of complications in T1D populations (63). A *post-hoc* analysis of DCCT data, based on capillary fingerstick glucose measurements, showed no association between within-day glycemic variability and the occurrence of microvascular complications (64).

Conversely, several studies, mainly on adult populations, have suggested a role of glucose excursions as independent risk factors for complications. Nerve excitability scores were inversely correlated with CONGA levels in a cohort of individuals with T1D (65). In a study on 37 adults with T1D, an association between glycemic variability metrics, including low blood glucose index and CONGA, and early structural damage of neuroretina was identified (66). Shen *et al.* detected an increased risk of distal symmetrical polyneuropathy among subjects with higher CV and MAGE (67). Cardiovascular autonomic neuropathy, a common and often misdiagnosed phenotype of diabetic neuropathy, has been associated with higher CV, SD, and MAGE in a case-control study (68). A link between glycemic variability and macrovascular disease has been also proposed, since an association between glucose SD and coronary artery calcium, a sign of subclinical atherosclerosis, was observed in cohort of men with T1D (69).

Limited studies are available regarding the long-term outcomes of glycemic variability during pediatric age. However, it is feasible that early consequences of glucose variability start during the first years of disease, regardless of the appearance of clinical manifestations. This hypothesis is supported by a cross-sectional study on 25 children with T1D, which found a relationship between greater glycemic excursions and oxidative stress, as measured by urinary excretion of 8-iso-prostanglandin F2-alpha (70). Oxysterol species, other biomarkers of oxidative stress, have been also found to be strongly correlated with glucose SD and MAGE (71). Moreover, findings from an *in vitro* study suggest that fluctuations in glucose levels may exert a more relevant influence than hyperglycemia alone on the activation of several genes associated with the development of microvascular complications (72).

Regarding long-term glucose variability, a retrospective analysis of electronic records of 1,195 children with T1D revealed an association between higher SD of HbA1c and microalbuminuria (73). In a cohort of 267 youths, lipoprotein-associated phospholipase A2, a marker of early vascular damage, was significantly associated with CV calculated from CGM data of a 4-week period (74). Additionally, masked hypertension, a cardiovascular risk factor defined as hypertension detected by continuous blood pressure monitoring with normal office blood pressure, has been detected more frequently in children and adolescents with T1D showing higher glucose SD (75).

Furthermore, long-term outcomes of high glucose variability are not limited to micro- and macrovascular damage, but a potential involvement of other organs, such as thyroid and periodontal tissue, has been described (76,77).

Cognitive disfunctions are closely related to suboptimal glycemic control in people with diabetes. A magnetic resonance spectroscopy investigation on human and murine models showed that brain glucose levels are strongly influenced by glycemic excursions (78). A metanalysis analyzing data from nineteen pediatric studies found that extreme blood glucose values are associated with poorer cognition and memory performance (79). Sleep quality has been also found to be negatively influenced by high glycemic variability during adolescence (80).

Lastly, metabolic control is fundamental for appropriate anthropometric development in children with T1D. Glycemic variability is likely involved in the linear growth process, as shown by a longitudinal study revealing an inverse correlation between height SD and glucose CV in 144 prepubertal children (81).

Strengths and limitations

The primary strength of this narrative review lies in its extensive coverage of studies on CGM data in pediatric populations with T1D, including real-world data. However, a notable limitation of this review is the current scarcity of long-term studies available to assess the impact of CGM-derived glycemic control indicators on the risk of chronic diabetes complications. Moreover, data availability is further constrained in pediatric populations due to the lower incidence of complications in this age group.

Conclusions

The widespread use of CGM systems has facilitated the characterization and quantification of glycemic fluctuations, thereby enabling the incorporation of glycemic variability

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as a useful therapeutic target in the routine clinical management of youths with T1D. This population is characterized by greater glycemic excursions related to behavioral and hormonal factors. While several studies suggest a potential role of glycemic variability as an independent risk factor for diabetes-related complications, additional long-term data are awaited to corroborate these findings. In this context, the increasing use of automated insulin delivery systems for the management of pediatric T1D represents a valuable treatment strategy to minimize the risk of glucose excursion in this population.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-114/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-114/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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