Continuous glucose monitoring has an increasing role in pre-symptomatic type 1 diabetes: advantages, limitations, and comparisons with laboratory-based testing

Abstract: Type 1 diabetes (T1D) is well-recognised as a continuum heralded by the development of islet autoantibodies, progression to islet autoimmunity causing beta cell destruction, culminating in insulin deficiency and clinical disease. Abnormalities of glucose homeostasis are known to exist well before the onset of typical symptoms. Laboratory-based tests such as the oral glucose tolerance test (OGTT) and glycated haemoglobin (HbA1c) have been used to stage T1D and assess the risk of progression to clinical T1D. Continuous glucose monitoring (CGM) can detect early glycaemic abnormalities and can therefore be used to monitor for metabolic deterioration in pre-symptomatic, islet autoantibody positive, at-risk individuals. Early identification of these children can not only reduce the risk of presentation with diabetic ketoacidosis (DKA), but also determine eligibility for prevention trials, which aim to prevent or delay progression to clinical T1D. Here, we describe the current state with regard to the use of the OGTT, HbA1c, fructosamine and glycated albumin in pre-symptomatic T1D. Using illustrative cases, we present our clinical experience with the use of CGM, and advocate for an increased role of this diabetes technology, for monitoring metabolic deterioration and disease progression in children with pre-symptomatic T1D.

Keywords: autoantibodies; continuous glucose monitoring; dysglycaemia; intervention trials; pre-symptomatic diabetes; type 1 diabetes

Introduction

Type 1 diabetes (T1D) is characterised by a long subclinical phase, with evidence of islet autoimmunity and beta cell loss detectable months to years before the development of dysglycaemia and clinical symptoms [1]. Islet autoantibodies can be identified in this stage of autoimmune activation and utilised to screen for and predict T1D risk [2]. The five recognised autoantibodies are glutamic acid decarboxylase (GAD), islet cell cytoplasmic (ICA), insulinoma-associated-2 (IA-2), insulin (IAA), and zinc transporter-8 (ZnT8) [3].

Stage 1 T1D is defined by the presence of multiple islet autoantibodies in an individual who is euglycemic. In
children, stage 1 T1D is associated with an 85% risk of progression to clinical T1D within 15 years [2, 4]. Stage 2 is characterized by glucose intolerance, while stage 3 T1D is defined by the biochemical criteria for diabetes mellitus in asymptomatic (stage 3a) or symptomatic individuals (stage 3b) [4, 5]. Accurate staging of the disease allows identification of at-risk children who will most benefit from interventions to prevent disease progression [6].

A clinical diagnosis of T1D is usually made at the onset of typical symptoms associated with hyperglycaemia including polyuria, polydipsia and weight loss in combination with a random blood glucose ≥11.1 mmol/L (200 mg/dL) or fasting blood glucose ≥7.0 mmol/L (126 mg/dL), confirming the diagnosis. However, in pathophysiological terms, this represents a late stage of autoimmune destruction with reduction of beta cell function to a degree which necessitates exogenous insulin replacement [1]. Interventions at this stage aim to control symptoms by re-establishing normoglycaemia and potentially preserve residual beta cell function [4]. To prevent progression to the point of requirement for exogenous insulin, requires identification of metabolic deterioration at an earlier stage [1, 7].

Laboratory-based tests such as the oral glucose tolerance tests (OGTT) and glycated haemoglobin (HbA1c) have been utilised in pre-symptomatic T1D for staging and risk prediction for progression to clinical T1D for many years. More recently, continuous glucose monitoring (CGM) – the frequent measurement of interstitial glucose concentrations using biomedical sensors – has been employed to detect early metabolic deterioration in T1D. Here we review the literature related to laboratory-based tests, and using illustrative cases, outline the value of, and advocate for an increasing role of CGM in the monitoring of pre-symptomatic T1D.

The oral glucose tolerance test (OGTT)

The OGTT-based criteria for stage 3 T1D is well-established but, in routine clinical practice, it is rarely required for the diagnosis in children [8]. Current clinical guidelines for staging in pre-symptomatic T1D rely on an OGTT to screen for dysglycaemia [9]. Within the research setting, various time-points in the OGTT have also been integrated with clinical (e.g. age, sex, and BMI) and laboratory (e.g. c-peptide, HbA1c, and IA-2A) metrics to calculate risk scores for progression to stage 3 T1D [10–14]. These scores have similar performance and, to date, no universal consensus has been established with regard to which of these risk scores should be implemented in the clinical setting. Though still considered the gold standard for T1D staging, the OGTT has significant limitations. It is confounded by significant day-to-day variability, requires multiple sample collections, is technically challenging to perform in young children (difficult intravenous access, inability to drink the glucose solution in a timely manner), and is not well accepted by families, particularly as repeat testing may be required for ongoing monitoring and staging [15].

Glycated haemoglobin (HbA1c)

Glycation refers to the post-translational nonenzymatic addition of monosaccharide (usually glucose) to the amino groups of proteins. Because glycation occurs continuously, the extent of protein glycation correlates with the average blood glucose concentration over the lifespan of the specific protein, and is the basis for the utility of glycated protein in diabetes as a marker of glycaemic control. Glycated haemoglobin (Hb), specifically HbA1c, has been the most extensively studied and clinically useful marker, but glycated serum proteins (fructosamine) and glycated albumin have also been utilized in certain clinical situations.

HbA1c

The maximum lifespan of erythrocytes is approximately 100–120 days with an average age at any given time ranging from 40–60 days, and as such, HbA1c reflects average blood glucose concentration in the preceding 8–12 weeks [16]. More recent plasma glucose concentrations contribute proportionately more to the HbA1c concentration – estimated to be 50% contribution from the previous 30 days, with 40 and 10% contributions from the previous 31–90 days and 91–120 days, respectively [17]. The glycation of HbA1c (like that of other proteins) involves an initial reversible reaction to form an aldimine or Schiff base (also known as Pre-HbA1c), which is then followed by an irreversible Amadori rearrangement with the formation of a ketoamine. From a clinical perspective, the short-term hyperglycaemia leads to the generation of significant quantities of Schiff base which reverses with normalisation of blood glucose concentrations. More persistent hyperglycaemia, however, leads to permanent attachment of glucose and the irreversible formation of the ketoamine from the Amadori rearrangement.

Clinical states associated with altered Hb turnover or erythrocyte survival [18], as well as haemoglobin variants [19] and recent transfusions, will affect HbA1c measurement and therefore clinical utility.

Although HbA1c ≥48 mmol/mol (6.5%) has been established for the diagnosis of diabetes, validation of this diagnostic threshold has been performed predominantly in the
adult type 2 diabetes (T2D) cohort [8]. HbA1c has also been included in the staging criteria for T1D, with a range between 39 and 47 mmol/mol (5.7–6.4 %) indicative of impaired glucose tolerance characteristic of stage 2 [8, 20]. Although highly specific, HbA1c demonstrates poor sensitivity for the diagnosis of early stage T1D [4]. It also lacks the ability to capture day-to-day variability in glycaemic excursions characteristic of the early stages of T1D.

A number of HbA1c-based criteria have been proposed to identify children at increased risk of progression to clinical diabetes. An earlier study demonstrated that a 10 % rise in a non-diabetic HbA1c on two consecutive occasions measured 3–12 months part was predictive for progression to stage 3 T1D with a median time of 1.1 years and a hazard ratio 5.7 [21]. This ≥10 % increase in HbA1c threshold has more recently been affirmed in The Environmental Determinants of Diabetes in the young (TEDDY) cohorts (hazard ratio [HR] 12.74, 95 % CI 8.7–18.6, p<0.0001) and TrialNet (HR 5.09, 95 % CI 3.3–7.9, p<0.0001) which also included additional factors (age, HbA1c at baseline, sex, maximum number of autoantibodies, and maximum rate of HbA1c increase by time of change) in a multivariable model [22]. The study also concluded that an increase of ≥10 % in HbA1c from baseline performed similarly to an OGTT 2-h plasma glucose for prediction of progression to clinical T1D. Other HbA1c-based criteria for progression to stage 3 T1D include: HbA1c >39 mmol/mol (5.7 %) [23] and two HbA1c >41 mmol/mol (5.9 %) [median time for progression 0.9 years, HR 11.9] [21].

Glycated serum proteins (fructosamine) and glycated albumin

Nonenzymatic attachment of glucose to amino groups to form ketoamines also occurs in proteins other than Hb – including serum proteins and membrane proteins. Fructosamine is the generic term for plasma protein ketoamines or 1-amino-1-deoxy-D-fructose [24], and more specifically is the measurement of the total stable irreversible serum glycated proteins at any given time. The half-life of serum proteins is significantly shorter than erythrocytes, and the degree of glycation is therefore more reflective of shorter-term alterations in plasma glucose concentrations – estimated to be 2–3 weeks, which is consistent with the half-life of albumin (20 days), comprising 80 % of total serum proteins [25].

The validity of fructosamine and glycated albumin as a reflection of the degree of serum protein glycation is affected by significant changes in protein concentration and/or half-life. Conditions associated with increased serum protein turnover, including nephrotic syndrome, protein-losing enteropathy, catabolism, as well as rapid changes in acute-phase reactants, result in falsely low fructosamine and glycated albumin levels, while states of reduced turnover (hypothyroidism and liver cirrhosis) result in falsely elevated levels.

Despite the development of improved methods for fructosamine and glycated albumin quantitation – including high-performance liquid affinity chromatography and liquid chromatography-tandem mass spectrometry (LC-MS/MS) – simpler and less expensive colorimetric and enzymatic commercial assays are most commonly used [26]. Generally, due to the potential for different methods and validation or verification procedures for the establishment of reference intervals used by clinical laboratories, is recommended that serial measurements are performed in the same laboratory with an understanding of performance characteristics and reference intervals for the specific assay. Studies have estimated that a 75 μmol/L change in fructosamine is equivalent to a 2 % and 3.3 mmol/L (60 mg/dL) change in HbA1c and plasma blood glucose, respectively [27].

Due to the lack of standardisation of methods for fructosamine and glycated albumin measurement, these glycemic markers are not recommended for the diagnosis of diabetes mellitus, but studies have suggested that an HbA1c of 48 mmol/mol (6.5 %) has been correlated to a fructosamine concentration of 255–290 μmol/L and a glycated albumin of 16.0–18.5 % [28, 29]. No fructosamine- or glycated albumin-based criteria for stage 2 T1D have been developed. Similarly, despite their reflection of shorter-term alterations in plasma glucose concentrations, they have not been utilised in prediction tools for risk of progression to stage 3 T1D.

Continuous glucose monitoring (CGM)

CGM systems have been shown to detect dysglycaemia in research studies investigating early stages of T1D and CGM metrics to predict risk of progression to clinical T1D have been published [30, 31]. Moreover, CGM can be used for monitoring glycaemic profiles in real-time and are more acceptable to children and their families than the OGTT or blood tests [31, 32].

Using illustrative cases, we describe our clinical experience with the use of CGM in pre-symptomatic stages of T1D, including advantages and limitations when compared to laboratory-based tests.
Methods

Islet autoantibody screening was performed using commercial ELISA kits for GAD, IA2 and ZnT8 (RSR Limited, Cardiff, UK). Children within the Queensland Children’s Hospital Diabetes Service who were identified as positive for multiple islet autoantibodies proceeded to an OGTT (if feasible) for T1D staging based on current guideline criteria. Those categorised as stage 2 or 3a T1D were offered intermittently scanned CGM (isCGM) for further monitoring. Participants were followed up in the Early Diabetes Clinic, specifically established to manage the cohort of children at risk of progression to clinical T1D. Families were counselled to remain vigilant for typical symptoms of diabetes and advised to confirm CGM readings >10 mmol/L (180 mg/dL) with fingerstick capillary blood glucose levels (BGL) using a glucometer.

The Abbott Libre flash glucose monitoring system was used (Abbott Diabetes Care Inc., Alameda, CA, USA) and participants completed a 14-day period of monitoring. Participants were instructed to ensure they scanned the sensor every 8 h to allow a continuous CGM trace to be available. The CGM target range to monitor for dysglycaemia was set as 3.9–7.8 mmol/L (70–140 mg/dL) in line with a previous study (10). CGM data were not blinded to the participant and family, but families were recommended to maintain their usual diet during the course of monitoring.

Cases

Clinical details for three cases, as well as T1D islet autoantibody screening and staging results are provided in Table 1.

Case 1

An asymptomatic 10 year old boy underwent sibling screening for T1D and was found to be multiple islet autoantibody positive. His staging OGTT demonstrated impaired glucose tolerance with a normal HbA1c (34.4 mmol/mol or 5.3 %). He was therefore diagnosed to have stage 2 T1D and commenced on isCGM monitoring. His baseline isCGM profile showed all sensor glucose (SG) values in target (euglycaemic) range (Figure 1A). Over the following 12 months he remained asymptomatic with an unchanged HbA1c however his isCGM profile showed increasing self-correcting postprandial glycaemic excursions following the consumption of high glycaemic index foods (Figure 1B). Overall, his glycaemic profile remained predominantly in the euglycaemic range. A repeat OGTT is planned for T1D re-staging.

This case demonstrates an ideal scenario of isCGM use in a highly motivated family with prior experience of T1D and understanding of diabetes technology, which benefitted both the family and the health care providers.

Learning points:
- Benefits of isCGM monitoring
- Enables remote monitoring of metabolic progression.

Table 1: Clinical details and T1D screening and staging results of illustrative cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, years</th>
<th>Gender</th>
<th>Reason for screening</th>
<th>Family history of T1D</th>
<th>Other autoimmune history</th>
<th>Signs and symptoms</th>
<th>OGTT</th>
<th>CGM</th>
<th>HbA1c, mmol/mol (%)</th>
<th>CGM target range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 M</td>
<td>Male</td>
<td>Sibling screening</td>
<td>NaA</td>
<td>Asymptomatic</td>
<td>Poor weight gain</td>
<td>912</td>
<td>N/A</td>
<td>34 (5, 3)</td>
<td>34–39</td>
</tr>
<tr>
<td>2</td>
<td>16 F</td>
<td>Female</td>
<td>Part of a prospective T1D screen study</td>
<td>Father with type 1 diabetes</td>
<td>Asymptomatic</td>
<td>History of hypothyroid disease</td>
<td>912</td>
<td>N/A</td>
<td>34 (5, 3)</td>
<td>34–39</td>
</tr>
<tr>
<td>3</td>
<td>10 F</td>
<td>Female</td>
<td>Sibling with T1D, random BGL, 10.7 mmol/L (193 mg/dL)</td>
<td>Brother with autoimmune disease</td>
<td>Asymptomatic</td>
<td>No polyuria or polydipsia</td>
<td>912</td>
<td>N/A</td>
<td>34 (5, 3)</td>
<td>34–39</td>
</tr>
</tbody>
</table>
Figure 1: Illustrative continuous glucose monitoring profiles. Case 1 (A) CGM profile at diagnosis of stage 2 diabetes, showing all sensor glucose values in normoglycemic range indicated by the % in target of 100% (shaded area), daily CGM traces (regular box), and graphical representation of average glucose level over a 24-h time period for the 2-week period of CGM monitoring (arrow). (B) CGM profile 12 months later showing occasional 5% time spent above target (shaded area), daily traces showing post prandial hyperglycemic spikes in sensor glucose values (yellow shaded areas), and graphical representation of average glucose level over a 24-h time period for the 2-week period of CGM monitoring with 95th percentile for average blood glucose level above target of 7.8 mmol/L (140 mg/dL) (arrow).
– Allows assessment of day-to-day glycaemic profiles under real-life circumstances such as post-prandial glycaemic effects of different foods.
– Reassures family that T1D is being closely monitored for progression without the need for repeated blood tests.

Case 2

A 2 year old girl with a strong family history of T1D, enrolled in a prospective diabetes screening and follow-up study, was found to be multiple islet autoantibody positive with an elevated random BGL and normal HbA1c. Baseline isCGM profile revealed significant post prandial glycaemic excursions with 36% of SG values being above 7.8 mmol/L (140 mg/dL). However, overnight and fasting glucose levels were within target range (Supplementary Figure S1A). The family were counselled regarding a high likelihood of progression to clinical T1D with requirement for insulin therapy. Two months later her HbA1c was unchanged at 39 mmol/mol (5.7%) and fructosamine concentration was 249 μmol/L (RR 190–285), however, the isCGM profile displayed 46% of SG values above 7.8 mmol/L (140 mg/dL) with prolonged post-prandial hyperglycemic glucose excursions and an average SG of 8.7 mmol/L (157 mg/dL). She had multiple SG readings >11.1 mmol/L (200 mg/dL) confirmed by finger prick BGL testing (Supplementary Figure S1B). Although she remained asymptomatic for polyuria and polydipsia, there were ongoing concerns about poor weight gain. The family were advised that their child had progressed to stage 3 T1D and decision was made to commence insulin utilising continuous subcutaneous insulin infusion (CSII) therapy with minimal basal insulin and prandial boluses. Following insulin initiation, her weight improved from −2.1 SD to −1.15 SD.

This case illustrates that isCGM can be useful in detecting the post-prandial glycaemic excursions seen in stage 3a T1D and can aid in diagnosing clinical T1D, particularly, in the setting of a normal HbA1c, which has limitations, particularly in detecting a short duration of hyperglycaemia and rapid evolution of T1D stages, as occurs commonly in onset in young children.

Learning points:
– isCGM data can assist in confirming stage 3 T1D and potentially obviate the need for multiple laboratory tests and an OGTT in children.
– Use of isCGM allows a child with an evolving clinical diagnosis of T1D to be safely monitored by the diabetes team remotely.
– isCGM data is informative regarding need for insulin initiation based on ongoing glycaemic assessments.

Case 3

An asymptomatic 16 year old female sibling of a child with known T1D was found to have a random serum glucose level of 10.7 mmol/L (193 mg/dL). Subsequent screening for T1D islet autoantibodies revealed significantly raised titres of GAD and IA2 with a normal HbA1c.

Baseline isCGM 14-day profile showed intermittent sharp fluctuations of SG values with stress and food (Supplementary Figure S2A).

Over the subsequent 3 months, there was an increase in the frequency of post-prandial glycaemic excursions, precipitating an independent decision by the family to restrict the carbohydrate content of meals (Supplementary Figure S2B). Her isCGM profile improved on the low carbohydrate meals, but insulin therapy was initiated to allow for normalisation of her diet.

She was initially commenced on meal-time only subcutaneous Aspart insulin to manage post-prandial glycaemic excursions, however, over the subsequent months a rapid deterioration in her glycaemic profile was noted, with persistently raised glucose values on isCGM (Supplementary Figure S2C). She therefore elected to commence on CSII therapy and required relatively low doses of insulin of 0.3 Units per kilogram per day to maintain euglycaemia.

This case demonstrates that isCGM can be a useful tool in monitoring the progression of a child from pre-clinical to clinical T1D and facilitates decision making regarding timing of initiation of insulin therapy.

Learning points:
– isCGM can be used to monitor rapid progression to clinical diabetes without the need for repeated OGTT at regular intervals for confirmation.
– isCGM allows diagnosis of clinical T1D in the pre-symptomatic phase and prevents metabolic decompensation and neurocognitive dysfunction.
– isCGM enables insulin initiation in a physiological manner with the potential advantage of initiating insulin at lower doses than in the setting of presentation with symptomatic T1D.

Discussion

The development and adoption of the staging system for T1D has enabled a better understanding and awareness of the trajectory of metabolic deterioration in pre-symptomatic individuals at risk [5]. Early identification and correct staging of individuals in the pre-symptomatic stages reduces the risk of metabolic decompensation and also allows the opportunity to identify individuals eligible to participate in
intervention trials aimed at delaying or slowing the progression to clinical T1D [7]. This is particularly relevant given the recent Food and Drugs Administration (FDA) approval of teplizumab, a humanised anti-CD3 monoclonal antibody, for the prevention of progression of stage 2 to stage 3 T1D.

As T1D screening programs in Australia expand to include the general population (https://www.kidsdiabetesscreen.com.au/) more individuals at risk of T1D will be identified and require accurate staging and monitoring. The use of CGM in these at-risk individuals will allow clinicians the opportunity to assess the glycaemic status of individuals in real-time, providing insight into factors affecting glycaemia in the real-world environment.

As utilisation of CGM in the monitoring and management of early T1D expands, it is important to acknowledge the significant contribution from professional organisations such as the International Federation of Clinical Chemistry (IFCC) Working Group on CGM (https://ifcc.org/ifcc-scientific-division/sd-working-groups/wg-cgm/) to standardisation efforts including the aim to establish traceability of CGM glucose values to materials and methods of higher metrological order [33], establish metrics for the evaluation of analytical performance of CGM [33–39] (including minimum acceptance criteria), and the proposed development of CGM guidelines analogous to international standards such as ISO 15197 [40].

Previous studies by the TEDDY group have demonstrated that involvement in an islet autoantibody screening study reduces parental stress and assists in coping with the diagnosis when T1D becomes clinically manifest [41]. However, there is significantly increased parental anxiety when the child is first detected to be at-risk for diabetes which can persist for many years [42, 43]. Hence appropriate psychological support should be available to families, as part of T1D islet autoantibody screening and monitoring programs. Most studies using CGM in autoantibody positive high-risk children have used blinding so that families do not have direct access to the real-time data, in an attempt to reduce anxiety and prevent inappropriate dietary manipulation.

The second and third cases presented here demonstrate the effectiveness of using CGM data not only to monitor metabolic progression but also to define onset of stage 3 T1D and guide therapeutic decision-making around insulin initiation. CGM enabled avoidance of OGTTs and provided insights to the children and their families of the effect of diet and exercise on glycaemic profiles, enhancing their understanding of the condition. Kontola et al. recently published their experience with CGM use in the Type 1 Diabetes Prediction and Prevention (DIPP) study and reported that CGM use was able to effectively diagnose stage 3 T1D and had comparable sensitivity to an OGTT [44]. As CGM devices become more precise and accurate, they may conceivably replace the OGTT for staging of T1D with the advantages of being less invasive, more acceptable to families and children, and allowing remote monitoring.

Recently, normative reference ranges for CGM metrics in autoantibody-negative individuals with normal glucose metabolism have been established, which will allow fine tuning of the CGM thresholds to define dysglycaemia in high-risk individuals [45, 46]. In the future CGM metrics may also potentially be used as an end-point for intervention trials to determine efficacy of immune-therapeutic agents [5, 47].

Although the usefulness of CGM to detect metabolic deterioration over time in individuals with early stages of T1D has been demonstrated in both the research and clinical setting, continued refinements in the monitoring protocols are necessary before there is broader adoption. Some principle aims in protocol development include the standardization of performing serial CGMs (reducing potential confounders such as diet, activity, inter-current illness, medications), and defining what CGM glycaemic parameters represent a significant change over time. An important CGM metric is the Glucose Management Indicator (GMI) [48] which is similar to an estimated HbA1c, but calculated using a new formula for converting CGM-derived mean glucose levels based on recent clinical trials and using the most accurate CGM systems. The GMI allows for evaluation of dysglycaemia over periods shorter than 3 months and therefore provides information about more recent metabolic deterioration. However, studies have identified discordance between HbA1c and GMI in both T1D [49] and T2D [50]. Despite this discordance, GMI is recognised as an important adjunct to the tools available in the monitoring and management of early T1D.

CGM metrics that could be used to differentiate between individuals who are likely to progress imminently from stage 2 to stage 3 T1D (progressors), and those with a much slower rate of progression (non-progressors) have been investigated. The Autoimmunity Screening for Kids (ASK) study found that individuals with more than 10 % CGM glucose levels >7.8 mmol/L (140 mg/dL) had a risk of progression to stage 3 T1D within a year of 80 % [31]. The TrialNet Pathway to Prevention (TN01) study demonstrated differences between progressors and non-progressors with regard to percent of CGM glucose levels above both 7.8 mmol/L (140 mg/dL) and 8.9 mmol/L (160 mg/dL) [31].

Glycaemic variability indices, including coefficient of variation (CV), standard deviation (SD), and mean amplitude of glucose excursion (MAGE), have been investigated as potential CGM metrics to identify progressors. The ASK study demonstrated that there were significantly higher parameters of glycaemic variability between progressors and non-
progressors [SD 1.5 vs. 0.9 mmol/L (27 vs. 16 mg/dL), CV 21 % vs. 15 %, and MAGE 2.4 vs. 1.4 mmol/L (43 vs. 26 mg/dL), all p<0.001] [31]. TN01 showed differences in SD [1.2 ± 0.3 vs. 1.1 ± 0.4 mmol/L (22 ± 5.4 vs. 19.2 ± 5.4 mg/dL), p=0.05] and MAGE [2.5 ± 0.6 vs. 2.1 ± 0.8 mmol/L (44.3 ± 9.9 vs. 38.4 ± 14 mg/dL), p=0.04] [31].

In conclusion, with increasing evidence for CGM metrics identifying individuals in the first stages of T1D who are at risk of rapidly progressing to clinical diabetes, the potential health economic benefits of DKA prevention and guiding the timing of initiation of insulin therapy, we advocate for an increasing role of CGM in pre-symptomatic T1D.

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Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

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