Review Article

Narrative review of the role of technology in pediatric diabetes: from testing blood glucose to subcutaneous automated therapy and hope for cure

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Background and Objective: Type 1 diabetes, the most common cause of diabetes in pediatrics, is defined by the hyperglycemia that results from the permanent autoimmune damage to the pancreas. The Diabetes Control and Complications Trial (DCCT) demonstrated that strict glycemic control targeting lower HbA1c goals can both delay the onset and progression of its complications that include diabetic neuropathy, nephropathy, retinopathy, and increased cardiovascular events. Our primary objective is to review the literature available regarding the technology applied for the treatment of diabetes, not only aiding patients' quality of life but addressing its effects on hypoglycemia and reduced risk of the long-term complications. It will synthesize the evolution of glucose monitoring devices; the development of insulin: from animal to recombinant engineering, smart insulin in the future; the development of algorithm-driven insulin delivery devices, the closed loop system/artificial pancreas; and the future utilization of technology to support islet cell transplant with the goal of a long-term cure. Emphasis will be made on what is known about the impact on its outcomes in children and adolescents.

Methods: A literature search was conducted using PubMed for publications from 1985 to present. Keywords used: type 1 diabetes, children, adolescents, pediatrics, continuous glucose monitoring (CGM), insulin pumps. Referenced articles include other reviews, current care guidelines as supported by cross sectional studies, cohort studies and randomized clinical trials.

Key Content and Findings: Understanding the pathophysiology of type 1 diabetes has led to the design of technology that facilitates glucose monitoring and insulin administration in a personalized manner. The current technology has improved outcomes and quality of life by decreasing hypoglycemic events and decreasing risk of long-term metabolic complications. Barriers remain, for children and adults, often driven by patient's preference as well as their understanding of the limitations of what they are wearing.

Conclusions: With the progressive evolution of this technology, it is now realistic to lower the burden of diabetes self-management while reducing hypoglycemia and risk of complications that otherwise impact daily life from academics, physical activity, career choices and even life expectancy.

Keywords: Diabetes technology; continuous glucose monitoring (CGM); continuous subcutaneous insulin infusion (CSII); insulin pump

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Introduction

The Diabetes Control and Complications Trial (DCCT) results have shifted the standard of diabetes management by transforming the concept of insulin dependent diabetes mellitus (IDDM, also known as type 1 diabetes mellitus) from a potentially lethal disease with decreased life expectancy to a better manageable chronic disease with normal life expectancy by preventing and reducing its complications. The DCCT demonstrated that strict glycemic control targeting lower HbA1c goals among patients with IDDM can both delay the onset of retinopathy, nephropathy, and neuropathy and slow the progression of existing microvascular complications (1). These ground-breaking results have raised the bar for clinicians, inventors, pharmaceutical and technology companies to improve the standard diabetes care, create better insulin hormonal replacement schedules, and improve the technology for monitoring blood sugar and delivering insulin.

The aim of this article is to discuss the role of medical technology in:

(I) Testing blood glucose;
(II) The development of insulin: from animal to recombinant engineering, smart insulin in the future;
(III) The development of insulin delivery devices;
(IV) Combining advanced continuous testing system with algorithm-driven smart delivery of insulin, the closed loop system/artificial pancreas;
(V) The future utilization of technology to support islet cell transplant with the goal of a long-term cure.

We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-145/rc).

Methods

A literature search was conducted using PubMed with keywords: type 1 diabetes, technology, children, adolescents, pediatrics, continuous glucose monitoring (CGM), insulin pumps. Years of publication range from 1985 to present. Referenced articles include other reviews, current care guidelines as supported by cross sectional studies, cohort studies and randomized clinical trials. These studies address not only the accuracy but also the effect of this technology on disease outcomes for the pediatric population (*Table 1*).

Discussion

Testing blood glucose

From office to home setting

Historically, testing glucose levels in the body to diagnose and monitor diabetes depended on urinary glucose. Ancient civilizations and cultures recognized that the sweet taste and smell of urine was a feature of diabetes, which was considered for a long time a kidney disease (2). The development of biochemistry analysis of glucose continued throughout the early 1970s and was the only method to monitor diabetes at the physician's office. A urine test strip concept was also introduced for easier access to test in the home setting. The same concept was applied to test strips to measure glucose in blood utilizing the method of oxygen electrode. This concept evolved to create the glucometer with a biosensor which was based on a thin layer of glucose oxidase (GOx) on an oxygen electrode. The read result was related to the amount of oxygen consumed by GOx during the enzymatic reaction with the substrate glucose (3).

This concept has evolved dramatically over a few decades. It first revolutionized diabetes monitoring when portable glucometers made it possible to extend glucose testing from medical offices to the patients' homes.

Over the past few decades, glucometers became simpler, more accurate, more innovative, and less painful (physically and technologically) than any time before. Their approval for over-the-counter use depends on how they meet the standard of Accuracy as regulated by either the Food and Drug Administration (FDA) or the International Standards Organization (ISO) (4-6). FDA Accuracy criteria are that 95% of the values are within 15% of the reference method and 99% are within 20% of the reference method for the entire range of glucose values. ISO accuracy criteria are that 95% of the values are ±15 mg/dL from the reference method when the value is <100 or equal or greater than 100 mg/dL (7).

Current glucometer data can be transmitted by some smart phone apps, and can be shared easily with health care providers. Glucometers allow patients with diabetes to get more involved in their diabetes self-management and day to day decision making. It simply converted the diabetes care from sporadic clinic visits to a dynamic involvement and evaluation of glucose control at any point. However, the success of utilization of glucometer was always challenged by socio-economic determinants, literacy, and technology

Table 1 Literature search specifics

Items	Specification
Date of search	06/01/2022–06/01/2023
Databases and other sources searched	PubMed
Search terms used	Type 1 diabetes and technology, continuous glucose monitor, insulin pumps
	Filters: children, adolescents, pediatrics
Timeframe	1985 to present
Inclusion and exclusion criteria	Inclusion: human studies, randomized control trials, cohort studies, case control studies, reviews, care guidelines
	Exclusion: non-English
Selection process	Group effort with specific focus per individual

handiness (8).

In pediatric diabetes, falsification and fabrication of logbook glucose numbers became a common problem (9). Examples of compelling reasons for children doing this include: having to hide a dietary indiscretion or the result of a missed insulin dose that resulted from peer pressure situations. Secondary gain also plays a role. For example, an abnormal number in school, allows them to leave class. Children quickly were able to manipulate the glucometer system memory by removing its batteries, changing settings, or even using control solutions to test. This clearly shows that despite the advancement of technology, the human factor is still needed to utilize it correctly.

An additional advance in home monitoring came with urine ketone strip monitoring and blood ketone meters. The latter allow monitoring of blood ketones detection for screening and monitoring of ketoacidosis in the setting of hyperglycemia and illness and allow more accuracy than urine ketones. Such devices may reduce emergency department visits, hospital stays, and time to recovery from diabetic ketoacidosis (10).

From sporadic to continuous testing

The sporadic testing of glucose showed that collected data of glycemic control remained incomplete. Problems with unexpected hypoglycemic episodes, hypoglycemia unawareness, post-prandial glucose surges, brittle diabetes, and uncontrolled diabetes remain challenging to patients and physicians. Patients were not pleased with frequent finger pricks to keep testing glucose levels multiple times during the day or at night, when needed. A1c, reflecting an average glucose over 3 months, does not capture these events or glycemic variability. Ethnicity, anemia, pregnancy, iron deficiency and hemoglobinopathies can all confound A1c (11-14). The technology had to evolve and develop the concept of continuous glucose monitoring system (CGMS).

The first CGM was approved by the FDA in 1999 for physicians' professional use (15), then the concept was used for home use by patents in 2013. This technology utilizes interstitial glucose data collected every 1 to 5 minutes. The technology uses the same GOx reaction of glucometers via a needle-based sensor that is subcutaneously inserted in the abdomen, back of the upper arm or upper buttocks. The measurement given is rather a reflection of the plasma glucose from thirty minutes prior as a result of the time lag caused by the glucose filtration process into the interstitial space.

The initial CGM devices were approved for use as adjunct to glucometer use. In other words, patients were asked to confirm the reading of the CGM with the glucometer prior to making any therapeutic change (16). The newer generations of CGM are now reliable enough that patients no longer need to confirm readings with glucometer for treatment decisions (16). An accuracy within 20%/20 mg/dL of Yellow Springs Instrument (YSI) reference or with a mean absolute relative difference (MARD) of less than 10% allows for the making of treatment decisions that are not clinically different from the decision made by using self-monitoring of blood glucose (SMBG). The capacity of alarms for out-of-range glucose levels and the ability to follow numbers remotely by the CGMs is most attractive to parents of children with type 1 diabetes. This is in contrast with prior intermittent scanning models that had no alarms.

The initial approvals of CGM use were based on their capacity to reduce frequency and duration of hypoglycemic

events. These devices can now predict and give an alert when glucose values are rapidly decreasing in a time window of 30 minutes. This addresses the risk of adverse neurocognitive effects of hypoglycemia that particularly young children have (17).

Moving on from reduction of hypoglycemia as primary outcome, multiple studies have now shown improvement in A1c of about 0.5%, for either adults or children, over 6 months, albeit, predictably, largely dependent on user adherence (18-20). Having the data that an A1c of 7% or lower for adults and 7.5% or lower for children is related to decreased risk of microvascular complications per the DCCT (21,22), the task is to determine what that translates into in terms of degree and time spent in hyperglycemia and hypoglycemia to desired A1c and even more so if the technology is also to address the limitations of A1c measurement (23). This solidifies the utility of CGM. With data every 5 minutes, it has become a matter of time spent in range, hyperglycemic or hypoglycemic.

The International Consensus of Glucose Monitoring was published in 2017 to offer guidance to clinicians for more practical use in the clinical real-life setting (24). CGM reports have to include time spent in hyperglycemia, in range, in grade 1 and 2 hypoglycemia. The report needs to include at least 2 weeks of data, having been used by the patient over 70% of the time in that time frame. For non-older and no high-risk type 1 and type 2 diabetes patients, "very high" is defined as over 250 mg/dL, "high" is over 180 mg/dL, "in range" is defined as 70–180 mg/dL, "low" as below 70 mg/dL and "very low" is defined as below 54 mg/dL. Goals for these populations are respectively, less than 5% of the time very high, less than 25% of the time "high, 70% of the time in range (TIR), less than 4% of the time "low", and less than 1% of the time, "very low".

In 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress developed clinical CGM targets for type 1 and type 2 diabetes, pregnancy and older populations (20). Data addressing the correlation of CGM metrics to A1c included a cross sectional study by Beck *et al.* (24). Four studies were analyzed and on average, a time in the range of glucose of 70 to 180 mg/dL of 50% to 70% correlated with A1C of 8% and 7% respectively.

The assessment of the utility of CGM has evolved from adult to children overall; more recently it has narrowed to particular subgroups with known higher risk of glycemic control. One example is the adolescent and young adult group. Use of CGM over 6 months demonstrated greater reduction of A1c and increase in time range when compared to the traditional whole blood glucose monitoring irrespective of use of a pump or multiple daily injections and including patients with lower socioeconomic status (20).

There are currently four FDA approved, non-adjunctive, real-time CGMs. The two models by Dexcom, G6 and G7, are approved for ages 2 years and above (23,25,26), whereas the Abbott models, Freestyle Libre 2 and 3, are approved for ages 4 years and up (27). The Dexcom models, are designed for a 10-day duration. G6 is the only non-adjunctive sensor used in sensor augmented pump (SAP) for now. G7 has a shorter warmup period of 30 minutes than its predecessor that requires a 2-hour period. The Freestyle Libre models are approved for a 14-day duration. Freestyle libre 2 requires scanning of the sensor to view actual glucose numbers. Freestyle Libre 3 does not require scanning anymore and the warm up period is 60 minutes. The latest models of each brand are about the size of a penny, have customizable alarms, and are also approved for gestational diabetes and pregnancy as well. One non-adjunctive sensor, the Guardian, is used for the Medtronic models of SAP but the need to calibrate with four SMBG checks have caused this model to fall out of favor.

The Center for Medicare and Medicaid has eliminated the requirement of a minimum of four finger sticks in order to cover CGM's. While this has improved equity of care, economic barriers for private payor patients and challenges of wearability logistics remain. Children are less tolerant to wearing devices. Real life implementation varies greatly as well as parental fund of knowledge interpreting numbers and taking correct actions.

Smart watches have recently been developed and marketed to measure BG via a smart watch like sensor. Future developments include "smart necklaces" that may help monitor glucose levels through perspiration via a wireless sensor (28).

The development of insulin: from animal to recombinant engineering, smart insulin in the future

The discovery of insulin one century ago was the most important advancement in managing type 1 diabetes mellitus (29). Insulin was produced from both traditional mammalian pancreatic extraction, this caused clinical problems since humans produced antibodies to it, which interfered with clinical course of therapy, technology was ready to help and recombinant bacterial and yeast systems engineering helped creating human-like insulin (30). Furthermore, the technology was able to create different

types of insulin based on onset and duration of action. The long acting or basal insulins such as detemir, glargine and degludec, are designed to mimic background insulin production. The fast and short acting, also called bolus insulins, aspart and lispro, mimic the immediate pancreatic acute insulin release that occurs with a meal.

The development of insulin delivery devices

Limitations of subcutaneous insulin injections include the pain associated with injections as well as need for calculation of dosing. To help with burden of injections, insulin ports such as Medtronic i-port can be inserted into subcutaneous tissue to facilitate injection of insulin without the need to puncture the skin. They can be worn for 3 days at a time (31). Additionally, smart pens and smart insulin caps have been developed, which are Bluetooth enabled devices that can be used with insulin pens and cartridges. They are used in conjunction with a mobile app that allows bolus dose calculation based on pre-programmed parameters such as insulin to carbohydrate ratio, target glucose, and sensitivity factor. The app allows tracking of insulin delivery and well as provides trend data, alerts, and notifications. Insulin on board calculators helps prevent "stacking" of insulin doses (32).

Insulin infusion technology began in the 1970s (33), but did not become widely available until the 1990s and early 2000s. Continuous subcutaneous insulin infusion (CSII) or insulin pumps are medical devices in which rapid acting or ultra-rapid acting insulin is infused at a continuous rate throughout the day to mimic physiological pancreatic release of insulin, as well as bolus dosing for carbohydrate intake and glucose levels. Long-acting insulin is not required. Traditional pumps include 3 parts—subcutaneously applied insertion sets, tubing, and the insulin containing delivery device. Patch pumps have insulin contained in a "pod" which is inserted subcutaneously without need for tubing, and delivery is controlled via a separate wireless device.

In CSII, insulin is delivered as basal and bolus dosing. The basal rate is continuous delivery of insulin throughout the day, thus eliminating the need for long-acting insulin injection. Basal rates can be customized for time of day, physical activity, illness, dawn phenomenon and allows greater flexibility than subcutaneous dosing of long-acting insulin injections. Bolus doses are administered intermittently to treat hyperglycemia and for carbohydrate intake. Bolus doses can be administered with varying parameters based on insulin sensitivity, carbohydrate sensitivity, and target glucose for differing times of day. Bolus doses can also be extended to cover for certain foods that have higher fat content. These insulin delivery devices reduce the frequency of injections and also allow for smaller and more frequent dosing increments than insulin injections.

CSII has been shown to improve glucose control and to reduce hypoglycemic episodes (34). This therapy has been widely used in the past two decades with supporting guidelines from the European Society for Pediatric Endocrinology, The Pediatric Endocrine Society and International Society for Pediatric and Adolescent Diabetes, and American Diabetes Association (34,35). Insulin pump therapy offers a close resemblance to normal physiological insulin delivery due to the feasibility to change the basal insulin rate within circadian rhythms (36). It is clear now after two decades of using insulin pump therapy that it can provide improved glycemic control and better HbA1c levels when compared to traditional insulin deliveries (37-39). Some studies have also suggested that insulin pump can optimize postprandial glycemia (39), improve early angiopathy (40), preserve the residual β-cell function (41), even prolong the honeymoon period (42), and reduce risk of retinopathy (43). Most of the studies show that the long-term use of pumps does not increase the risk of hypoglycemia usually seen with traditional intensive insulin therapy (34,44). This is of great importance in pediatric populations prone to hypoglycemia such as toddlers with unpredictable feeding patterns or young athletes with vigorous exercise habits. The pump also allows better flexibility in dealing with Dawn and Somogy fluctuations of blood sugar by modifying basal rates at certain times of the night and early morning. The use of insulin pump therapy has increased dramatically in the past decade to include infants, toddlers and pre-school children (37), with many studies demonstrating improvement of metabolic control and HbA1c (38,39). This is probably related to the ability of the insulin pump to be flexible with pre and even post prandial dosing, as well as with basal rates to match unpredictable feeding and activity levels in this group age. Multiple insulin-to-carbohydrate ratios and correction factors can be set for different meals or times of the day. Patients can have different profiles for different days depending on their activity schedules. Temporary increased or decreased basal rates can be set depending on higher or lower requirements. For example, illness can lead to hyperglycemia or exercise can lead to hypoglycemia.

Adolescents have always been considered a good target for insulin pump therapy to match their lifestyle and to help in changing their body image (40). Many studies have shown improvement in the quality of life of adolescents and young patients with type 1 diabetes (41,42).

However, since the insulin pump is a technical device, potential problems can be related to misuse or malfunction. Preparatory education and particularly assessment of patient commitment and competence are essential before starting a pump regimen. Limitations include batteries failing, tubing getting kinked, insulin reservoirs leaking, needles slipping, or software malfunctioning (45). Diabetic keto-acidosis (DKA) and severe hypoglycemia may occur in early stages of pump use (34) due to inability to identify above mentioned mishaps, but repeated DKA episodes may continue due to patient rejection and disconnection of the pump (e.g., first case). Hypoglycemia can occur if the pump's tubing is primed with the pump being connected, or repeated boluses for one meal are given. Low socioeconomic status is a well-known factor affecting diabetes metabolic control and it remains a major factor even with intensive insulin treatment (46). A study by the FDA in the USA, documented 13 deaths due to severe hypoglycemic or hyperglycemic episodes related to malfunction of the pump. Two of these death cases were possible suicide attempts (47). Screening for malfunction in the device and psychological symptoms in the patient should become standards of diabetes care with pump therapy. Additionally, this technology can have cybersecurity vulnerabilities with potential of hackers manipulating insulin dosing (48).

There are also adhesive reactions, lipo-hypertrophy from continuous insulin infusion, and risk of infections. Additionally, the visibility of the pump device can be a source of unwanted attention or body image concerns to the patient.

Discontinuation of the pump therapy in pediatrics can happen at patient and family preference. Age at diagnosis, duration of diabetes pump therapy, rate of hypoglycemia and DKA episodes as well as pubertal status are factors that may influence pump acceptance and competence. Prior adherence to general diabetes management and compliance with therapy play a major role in motivation to continue pump therapy (49). Pump therapy will fail if it is considered by the patient and family as a magic solution to "cure" diabetes without meticulous bolus and basal rate adjustment. Thus, the selection of motivated patients and family, providing detailed carbohydrate counting training, availability of continuous education, monitoring of insertion site to prevent and treat infections and support according to standard pediatric diabetes care, are essential steps to make insulin pump therapy successful (50,51). Dealing with parental challenges and providing support education is needed for all age groups of pediatric diabetics on pump therapy (52). It also requires the availability of trained staff to perform this education.

Combining advanced continuous testing system with smart delivery of insulin, the closed loop system/artificial pancreas

The future of insulin pump therapy in pediatric diabetes sounds promising. The advent of SAP therapy based on continuous blood glucose monitoring allowed suspension of insulin delivery based on CGM data (53). In 2009 the MiniMed 530G was the first CSII with low glucose suspend (LGS). This technology suspends delivery of insulin when glucose values determined by CGM fall below a preset threshold. Studies demonstrated reduction in hypoglycemia without increase in hyperglycemia (54). In 2015, the Tandem T:Slim with Basal IQ was released with predictive low glucose suspend which utilizes CGM data to suspend insulin delivery when glucose values are predicted to fall below present threshold in the next 30 minutes.

The association of SAP, wireless technology and intensive insulin therapy seems to foreshadow the future of an artificial pancreas (55).

Advances from SAP to automated insulin delivery (AID), also referred to as hybrid closed loop (HCL) allows adjustment of insulin delivery based on CGM Data by a software algorithm. AID systems connect insulin pumps, CGM data, and software algorithms to automate insulin delivery based on real-time glycemic data (56). AID has been shown to increase TIR (57,58). In two meta-analyses of randomized controlled trials with children and adults with type 1 diabetes, use of AID, compared with conventional therapy, was found to increase glucose TIR by 11.1% and 8.5%, and hypoglycemia was reduced by 1.9% and 1.3% (48). The first available AID was the Medtronic 670G in 2016 and now 770G with Guardian sensor. Limitations such as difficulty staying in automated mode, need for sensor calibration, and persistent alarms limited use (56). In 2020 the Tandem T:Slim X2 with Control IQ with Dexcom G6 was released. The T:Slim X2 insulin pump has basal rate modulation with preset targets. The newest AID at the time of publication is the Omnipod 5 with Dexcom G6 that was released in 2022. Insulin is delivered in "micro-boluses" delivered based on CGM data and

algorithm based on total delivered insulin. Target glucose can be adjusted allowing further customization. Currently it is indicated for age 2 years and above. Additionally, this is the only AID system that can be fully operated by smartphone and the first tubeless AID (56). Omnipod 5 pivotal trial showed increased TIR as well as decrease in hypoglycemia risk (59).

As many patients awaited availability of HCL technology, do-it-yourself or open-source systems were developed, which use refurbished insulin pumps with software to help interface the pump and CGM. These are not currently FDA approved but are seen in clinical practice.

Additionally, the iLet Bionic Pancreas, is an AID system in development that will require weight and target glucose, but will otherwise require minimal user input for carbohydrates. The pivotal trial showed improvements in A1c, TIR, and 0.5% decrease in A1c (60). There are trials ongoing of "bionic pancreas" or dual hormone delivery systems with both insulin and glucagon (61).

Insulin pump therapy has evolved dramatically in the past two decades. It can definitely provide an improvement of glycemic control in all pediatric age group. Its flexibility with basal and bolus rates helps match the feeding needs of infants, toddlers and pre-school children and the active lifestyles of adolescents with type 1 diabetes.

However, physicians need to realize that insulin pump therapy may not be effective for everyone. The motivation and dedication of patients and families to diabetes management before pump prescription is the best predictor for insulin pump success. Psychological problems such as rejection of the diagnosis of diabetes mellitus, which cause prior poor control, will sabotage pump therapy as well. The education, psychological support and monitoring of diabetes care should continue throughout therapy.

As technologic knowledge increases in the next generation it will not only make the use of pump therapy more widespread, but also will help further to advance toward making the artificial pancreas a successful project in the future. However, patient selection, support, and education will still be primary determinants of success.

HbA1c, DKA, and severe hypoglycemia were lower with use of CSII and/or CGM (62).

Burdens of technology

Technology can be beneficial but can also be overwhelming for patients and family. Initial as well as ongoing education, troubleshooting technology, upgrades can be burdensome. There are also multiple alerts and reminders that can be overwhelming. Privacy is a concern for adolescents. Diabetes burnout is prevalent in the population and while technology can help in certain aspects, may also contribute in other ways. The device can be a physical reminder of their chronic condition.

The future utilization of technology to support islet cell transplant to have insulin-free diabetes/cure

One of the major historical challenges in islet cell transplantation is the immune mediated destruction of the graft requiring the need for chronic immunosuppression with its toxic effect (63).

Encapsulation of pancreatic islets allow encasing the pancreatic islet cells within a protective device to ensure their viability. The use of technology has created devices made of a semi-permeable material which permits the exchange of glucose, oxygen, nutrients, metabolic waste, and insulin, but prevents the entry of immune cells or antibodies (64).

Macroencapsulation that involves encapsulation of multiple islets within a device, microencapsulation that involves encapsulation of each individual islet within its own device (64).

This advancement in medical technology created a 'bioartificial pancreas' (64) compared to a 'technical pancreas' which refers to the closed loop system.

Conclusions

Technology has proven to have a fundamental role to aid patients and families with the self-management of diabetes. It has proven beneficial in improving hypoglycemic events and overall glycemic control. As the access to these devices increases, we hope this review helps Endocrine and Non-Endocrine medical professionals become more familiar with these and support patients' empowering in their care. Devices are now of smaller size, improving wearability. AID, with the aid of accurate and predictive CGM, is alleviating the burden of constant decision making by the patient. Patients' education would continue to be paramount for interpretation and benefit so that real life circumstances mimic the outcomes of the controlled studies.

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