REVIEW ARTICLE

Type 1 diabetes mellitus management in young children: implementation of current technologies

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The use of advanced technologies for diabetes management is on the rise among pediatric patients with type 1 diabetes (T1D). Continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring, predictive low glucose suspend, hybrid closed-loop insulin delivery systems—all enable better diabetes management and glycemic control. However, when used by children, and especially very young children, specific aspects must be taken into consideration, including technical parameters, ease of use, parental stress, and satisfaction. The unique characteristics of T1D in children aged <6 years are reviewed and studies of the pros and cons of different technologies in this specific age group are presented. Addressing such issues when implementing advanced technologies among very young children with T1D will enable better diabetes management and will hopefully ease a tremendous burden of both children and families.

INTRODUCTION

The incidence of type 1 diabetes (T1D) is increasing worldwide by an estimated rate of 2–5% per year. Past studies documented the greatest increase in children aged <6 years.[1] The EURODIAB study, which included 26 centers from 22 European countries, showed an annual increase of 3.4% in T1D between 1989 and 2013 among children aged <14 years. Data from the United States from the SEARCH for Diabetes in Youth Study also showed an increase in annual incidence of 1.8% between 2002 and 2012.[2] However, in the SEARCH study after adjusting for age, sex, and ethnic group, an increase was identified in all age groups *except* children aged 0–4 years.[3]

The present report describes the unique characteristics of T1D in this age group, the challenges posed, and the available technological solutions, which can hopefully ease management for parents and caregivers.

Characteristics of T1D in young children
The characteristics of T1D differ between very young children and older children and adolescents. The classic symptoms of diabetes may be subtle and difficult to distinguish from other acute illnesses at a young age until the disorder has progressed to frank ketoacidosis. Indeed, a higher percentage of young children may present with diabetic ketoacidosis (DKA) at disease onset.[4] Furthermore, younger children have more severe metabolic decompensation at onset of diabetes, with both lower C-peptide levels at diagnosis and rapid deterioration of C-peptide secretion thereafter. Diabetes diagnosed at a younger age is associated with higher levels of auto-antibodies and a higher susceptibility for the disease in first-degree family members.[5] One study showed that siblings of children diagnosed before age 5 years had a 3–5-fold higher cumulative risk of

acquiring T1D by age 20 years than siblings of children diagnosed at ages 5–15 years.[1] The presence of DKA at diagnosis of T1D in children has been found to be associated with less favorable long-term glycemic control as assessed by glycated hemoglobin (HbA1C) and the rate of DKA episodes.[6,7] Therefore, young patients presenting with DKA may need more stringent treatment and closer follow-up.

Targets for glycemic control
Targets for glycemic control in very young patients with T1D have changed over the years mainly because of fear of hypoglycemia. The 2019 American Diabetes Association guidelines set the HbA1C goal at <7.5% for all pediatric age groups.[8] It has been shown that lower HbA1C levels can be achieved in children aged <6 years, without an increased risk of hypoglycemia.[9] In patients diagnosed with T1D at preschool age, the mean HbA1C level in the first year is a strong predictor of achieving the target HbA1c level in subsequent years, regardless of the type of insulin regimen.[10] This "metabolic tracking" emphasizes the importance of achieving early optimal control even in younger children.

Role of environmental factors in glycemic control
Very young children require only small amounts of insulin owing to their high insulin sensitivity and low body weight.[11,12] However, several behavioral and developmental factors pertinent to this age group may impede the achievement of glycemic control targets. The unpredictable eating habits and periods of high physical activity in young children in addition to their limited ability to communicate their symptoms, make the recognition and early prevention of hypoglycemia difficult. According to Mortensen and Hougaard,[13] this may partly explain the higher likelihood of severe hypoglycemia in younger children with diabetes.

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Role of the parents in achieving glycemic control

In the very young age group, it is up to the parents/caregivers to manage the disease. Impediments to good control include parental stress, parental guilt that the child is "missing out" on normal age-appropriate activities and has to deal with a chronic illness, and especially, parental fear of hypoglycemia. Child–parent interactions also have an important place in this dynamic.[14] The proper development of children is known to depend largely on the ability of the parents to be authoritative, to place and maintain proper borders, and to mitigate their reactions to their child's behavior. All these factors are even more important when the child has a chronic illness, such as T1D.

Effect of poor glycemic control on development

Severe or chronically poor glycemic control early in the course of T1D has a profound impact on cognition and brain structure, particularly in very young children. Dysglycemia (hyper or hypo) interferes with crucial processes in the developing brain such as neuronal proliferation, myelination, and synapse formation.[15] One study found that, although there was no significant difference in cognitive function between children with T1D and healthy controls, stratifying the subjects by age at diagnosis yielded significantly poorer results for intelligence quotient, attention, and psychomotor efficiency in the patients diagnosed before age 7 years.[16] On stratification by glycemic control, the children with hyperglycemia had lower general cognitive abilities, slower fine motor speed, and lower receptive language scores. Similar differences were noted when adults diagnosed very early in life were compared to healthy controls.[15,16] Preschool children with T1D and poor glycemic control also showed structural brain changes consisting mainly of lower white and gray matter volumes, in line with the well-known vulnerability of the brain in young children.[15–18]

CURRENT TECHNOLOGIES IN T1D MANAGEMENT

Advanced technologies have become an integral part of T1D management. They include continuous subcutaneous insulin delivery (CSII), continuous glucose monitoring (CGM), sensor-augmented pumps (SAPs), predictive low glucose insulin suspension (PLGS), and closed-loop systems. Their use can help to attenuate and perhaps overcome many of the problems that very young children with T1D and their families face daily. Although various studies have included very young children in their cohorts in recent years, current clinical evidence-based guidelines in this unique age group are partial.

The aim of the present manuscript is to review current technologies with emphasis on the advantages and disadvantages of each that are pertinent to the young age group as well as their psychological impact on the family unit.

Continuous subcutaneous insulin delivery (insulin pumps)

The past 30 years have witnessed the growing use of CSII for insulin replacement therapy. Recent data from the T1D Exchange showed that insulin pump use increased from 57% to 63% between 2010–2012 and 2016–2018 with the largest increase being in very young children (an increase from 50% to 60% in this age group).[19] CSII has been shown to be more accurate in imitating the normal physiology than multiple daily injections (MDIs), consequently providing better metabolic control.[20] It allows for the precise titration of insulin levels, definition of different insulin–carbohydrate ratios, and insulin sensitivity factors for each time of day, and higher flexibility in food and activity. A 2010 Cochrane review summarized the findings of 23 studies comparing CSII with MDIs; 7 were conducted in patients aged <18 years, although there was no specific reference to the different pediatric age groups.[21] The results showed that CSII was better than MDIs for achieving glycemic control, but the differences in

HbA1C were marginal, and treatment with CSII did not reduce overall rates of hypoglycemia.

Studies focusing specifically on very young children with T1D found CSII treatment to be feasible in this age group, with no association with an increase in hypoglycemic events or DKA.[22,23] The European multicenter PedPump study assessed the use of CSII in children under real-life conditions.[24] Data of >1000 patients aged 0–18 (average age 11.8 ± 4.2) years were recorded for 90 days. Preschool children accounted for approximately 15% of the cohort. Glycemic control with CSII was found to be better in preschool than in older children, and the more the boluses given, the better the HbA1C. The investigators concluded that CSII is useful for achieving glycemic targets, especially in young children with a low incidence of hypoglycemia or DKA (6 events per 100 patient-years for both).

A position statement published in 2006 recommended that all very young children with T1D should be considered for CSII treatment.[25] It also emphasized the need to coordinate expectations between the physician and caregiver as well as the need for caregivers to participate in preparatory teaching sessions on the use of CSII. The following year, the European Society for Pediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes published a consensus statement (endorsed by the American Diabetes Association and the European Association for the Study of Diabetes) based mostly on observational studies.[20] It suggested that CSII use in the young pediatric age group decreases the frequency of severe hypoglycemia, leads to improved HbA1C levels (according to one retrospective control trial), and is associated with at least a similar quality of life to MDIs for patients and their families. The 2017 International Society for Pediatric and Adolescent Diabetes guidelines for managing diabetes in preschool children clearly state that pump therapy is the preferred method of insulin administration for children aged <7 years.[26]

Nevertheless, the impact of CSII on glycemic control in the very young age group is not clear-cut.[27] Whereas two large registry studies showed a significant decrease in HbA1C in patients treated with CSII compared with MDIs,[28,29] two other studies either failed to note improved glycemic control among young CSII users[30,31] or found a decrease in HbA1C across all participants, with no differences between the CSII and MDI groups.[32] One study reported a significant decrease in HbA1C with a reduction in severe hypoglycemic events, without an increase in DKA.[12,33,34] The largest study including >2500 children with T1D aged <6 years, published in 2014, compared clinical outcomes based on the US T1D Exchange and the German/Austrian DVP registry.[9] Pump use was significantly more frequent (74% vs. 50%, $p < 0.001$) and HbA1C levels lower for patients in the DPV registry. However, the lower HbA1C level in the DPV study was significantly lower in both CSII and MDI users, and there was no significant between-group difference in severe hypoglycemia, although the patients in the T1D Exchange registry had more DKA events. Thus the differences in glycemic control could not be solely attributed to the differences in the mode of insulin delivery.

It is noteworthy that overall parental satisfaction with CSII is usually very high, up to 92% according to some studies.[23,31] One of the greatest benefits reported by parents is a reduced fear of hypoglycemia. Other advantages noted were the elimination of painful injections, easier control of meals, fewer restrictions on the frequency, timing and carbohydrate contents of snacks, fewer confrontations during mealtimes, availability of bolus calculators that conferred a sense of control, and overall improvement in family life.[35,36] Most of the parents chose to continue using CSII at the end of the study period.[34,37]

However, some found that using CSII either did not lessen their stress levels or caused added stress and an exaggerated number of blood glucose measurements.[37] Parents expressed their need

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for more education and physician support in order to address these concerns.[25,32,35]

CSII use by any person with diabetes requires the acclimation of both patient and family. This is particularly hard for children because of both their young age and low body weight. The reasons cited by older children for discontinuing pump use include an increased sense of disease, embarrassment in front of peers, discomfort due to the constant attachment of the pump to the body, painful needle insertion, difficulties during sports activities, and fear of hypoglycemia.[38,39] It is noteworthy that they did not mention difficulties with the technicalities of pump operation or frequent occurrence of hypoglycemia.[38,39] In very young children, these problems are magnified by the size of the device (which is not individually tailored), the limited types of clothing that are compatible with pump carriage, and the vigorousness of their physical activity.

Moreover, the small amount of total daily insulin and, consequently, basal insulin needed in young children makes them more prone to catheter occlusions. Some insulin pumps do not allow for small increments, adversely affecting dosing accuracy.[40] The majority of studies on the applicability of CSII in young children with T1D have so far been limited in duration and sample size. The consistently promising findings of improved glycemic control and quality of life in CSII users in general justify further studies in the young pediatric population.

Continuous glucose monitoring
CGM may serve as a synergistic tool with CSII or as a novel stand-alone technology. It provides a bird's eye view of glucose levels rather than a narrow point-by-point examination. The ability to observe patterns and trends eases both daytime bolus dosing and overnight control for patients and parents, and the continuous data provide them with a better understanding of the effects of different foods and activities.[41] CGM has a particularly important place in the treatment of young children who cannot appropriately communicate their feelings during hypoglycemia/hyperglycemia nor can they react to hypoglycemia.[41]

The conclusions of most randomized controlled trials of CGM technology agree with the 2012 Consensus Statement that CGM is appropriate for use in children of all ages provided they are properly motivated and receive proper guidance and education from the medical team in order to make the most of the available data.[41] The greatest effects were noted when CGM was used on a near-daily basis. For children aged <7 years, the 2017 guidelines of the International Society for Pediatric and Adolescent Diabetes recommend CGM with alarms as the preferred method for monitoring glucose levels.

The reported inaccuracy of the currently available sensors during euglycemia and hyperglycemia ranges between 8% and 13% and, during hypoglycemia, between 15% and 20%.[42] These findings are explained by the rapid glucose exchange between extracellular and intracellular fluids during hypoglycemia. The low accuracy rate during hypoglycemia remains a technological challenge as well as an important disadvantage of CGM, especially in young children.[43] The data from the T1D Exchange between 2016 and 2018 showed that children had an increase of >10-fold in CGM use (from 4% to 51% in children aged <6 years).[19,44] Although connecting to CGM is safe in the young age group, the duration of sensor wear during the day may decrease over time.[45,46] One of the major disadvantages impeding continuous sensor use are the frequent dermatological complications of young children's delicate skin.[47]

However, the recent "Strategies to Enhance New CGM Use in Early Childhood (SENCE)" study presented at the 2019 American Diabetes Association scientific meeting did show improved parental satisfaction with CGM use. The study examined the effect of CGM use among very young children (age 2–7 years) with T1D on time in range. The study that included 143 children randomized into 3 groups (SMBG, CGM, CGM+parental education) showed that, over the study course, CGM+parental education led to better time in range along with improvement in familial quality of life.[48]

CGM is advantageous for caregivers because the ongoing data provided in addition to the alarm warning when glucose levels decrease can attenuate their fears of hypoglycemia, an important factor in poor glycemic control in the pediatric age group. Food and Drug Administration approval of the Dexcom G5 CGM for insulin dosing decisions may have provided caregivers with additional reassurance.[42]

A recent study addressing the benefits and challenges of CGM use among very young children with T1D analyzed interviews with parents of children aged 1–8 years using CGM. Parents described a decrease in overall worrying, improved sleep, improved time in range, and better decision-making in diabetes management as pros of CGM use. On the other hand, the difficulties of wearing a device on the child's small body, skin irritations, and over-whelming constant information were cons of CGM use.[49]

Studies have also shown that caregivers often fail to address attention to the sensor until they arrive at the diabetes clinic; thus a great deal of information is lost between physician follow-up appointments. This factor may also partly account for the failure of some studies to find an association of CGM use with improved HBA1C levels in young patients.[43] It should also be noted that some parents of children with T1D found that CGM use either did not attenuate their fear of hypoglycemia or actually increased it at night.[46,50]

Possible reasons might be recurrent alarms and/or constant knowledge of the child's glucose level, which may exacerbate anxiety among some parents. Flash Glucose Monitoring (FGM; FreeStyleLibre) consists of a subcutaneous sensor that stores blood glucose levels continuously on a separate reader. Studies of FGM use in older patients reported a reduction in HbA1C, with fewer episodes of hypoglycemia and high satisfaction.[51] Patients using FGM were shown to administer boluses prior to meals much more frequently. The FGM system is easy to use, accurate, requires no calibration during the 14-day lifespan, and is relatively inexpensive in some countries (depending on national health insurance plans). In 2016, the system was approved for dosing decisions, but only for patients aged >18 years.[42] Its major current disadvantages are the lack of alarms during hypoglycemia or hyperglycemia, although the new generation of the FGM will also provide alarms, as well as lack of interaction with insulin pumps.[52,53]

A recent multicenter study in the UK was conducted to determine the accuracy, safety, and acceptability of the FGM in children.[51] The cohort consisted of 89 patients aged 4–17 years followed for 2 weeks. Sensors were masked to the participants and compared with self-monitoring blood glucose measurements. The results showed that FGM was relatively accurate, with an overall mean absolute relative difference of 13.9%, regardless of patient age, weight, or sex, or method of insulin administration. Another recent study of FGM use in children from Poland was conducted during 12 days of summer camp with participants aged 8–18 years.[54] The overall mean absolute relative difference ranged from 12.9% to 13.5%; in those with a stable glycemic state, values ranged from 10.4% to 11.4%. The investigators concluded that the system is safe in children, but its accuracy depends on the glucose trend.

Sensor-augmented pump
The use of CGM and CSII has a synergistic effect on glycemic control. Studies of the use of SAP in children aged <7 years reported significant improvement in those with a higher baseline HbA1C (>7.5%), although all caregivers expressed overall satisfaction.[23] The most important benefit was the reduced fear of hypoglycemia. There are several ongoing clinical trials comparing

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closed-loop technologies with the SAP in the pediatric age group, but only patients aged ≥10 years are included.

Predictive low glucose insulin suspension
PLGS is an advanced feature of SAPs that halts insulin infusion when glucose levels decrease quickly and/or reach a preset value. When levels begin to rise again, insulin infusion is automatically reinstated. An in-home randomized trial assessing the efficacy and safety of the PLGS system in children as young as 4 years reported a significant reduction in median nighttime glucose levels <70 mg/dL. This benefit came at the expense of a higher mean glucose level but not a higher morning glucose level.[55] A recent randomized study in older children also showed significantly fewer hypoglycemic events in the intervention group during both day and night.[56] In this study as well, mean glucose levels were higher. However, an assessment of extended interruption of CSII as part of an overnight closed-loop glucose control study in children and adolescents found that the prevention of hypoglycemia did not coincide with an increased risk of hyperglycemia.[57] In very young children, this parameter is critical owing to the deleterious effects of hypoglycemia on brain development as well as the high level of parental fear of hypoglycemia, which is often associated with poor glycemic control.[50]

A longitudinal, multicenter trial of the threshold suspend feature of SAP is currently being conducted in children aged 5–17 years. The study will last 1 year and is expected to include 200 participants. The outcome measure is the change of HbA1C from baseline (https://clinicaltrials.gov/ct2/show/NCT02120794?term=sensor+augmented+pump&cond=type+1+diabetes&age=0&rank=5).

Another group is currently recruiting children aged 6–14 years for an open-label single-center randomized crossover study comparing SAP with PLGS to CSII with FGM. The primary outcomes are time in range and rate of hypo/hyperglycemia; secondary outcome measures are the effect on sleep and quality of life of the children and their caregivers (https://clinicaltrials.gov/ct2/show/NCT03103867?term=sensor+augmented+pump&cond=type+1+diabetes&age=0&draw=2&rank=19).

Closed-loop system (artificial pancreas)
The epitome of diabetes technology is the rapidly evolving closed-loop system, which aims to provide optimal diabetes management using smart algorithms that require minimal user input. A randomized controlled trial compared nighttime glycemic control and meal glycemic response between a closed-loop system and standard pump therapy in 10 patients aged <7 years.[58] The closed-loop system was associated with a trend for more time in the target glucose range (primary outcome measure), although the difference from the pump was not statistically significant. The improvement in degree of hyperglycemia, the secondary outcome measure, was significant, with no increase in the rate of hypoglycemia.

Another study of closed-loop technology in children aged 3–7 years examined differences in diluted vs. standard insulin delivered by pump. Use of the closed-loop system allowed for good overnight glucose control. Children in the diluted insulin group had reduced glucose variability. However, the study's conclusions were limited by the very small cohort, which is a limitation of many closed-loop studies in both children and adults.[59]

The same group recently published results of a larger open-label, multicenter, multinational, randomized, crossover study aiming to assess both the feasibility and safety of hybrid closed loop (HCL). The study was conducted among children aged 1–7 years with T1D in seven European hospital diabetes clinics and again compared HCL using diluted insulin vs. HCL using standard insulin during unrestricted living over two periods, each 3 weeks long. The study showed no differences in mean glucose levels, glucose variability, or total daily insulin delivery. No adverse events such as severe hypoglycemia or DKA occurred during the

study period. The investigators concluded that unrestricted home use of HCL is both feasible and safe among this very young population.[60]

Following this study, the experience of the children's families was evaluated via questionnaires. Topics such as reduced diabetes management burden, improved sleep quality, and less time invested in diabetes management were reported. Parents did point out that size of the device and connectivity problems were areas needing improvement.[61]

Another randomized crossover study evaluated the safety and performance of the artificial pancreas in children aged 5–8 years.[62] Children used either the artificial pancreas system on an outpatient basis or their usual CSII+CGM systems at home over two 68-h periods. Those in the artificial pancreas arm who completed the study showed a significantly increased time in range and lower mean glucose levels. Hypoglycemic events were similar in the two groups, and there were no other adverse events.

The safety and efficacy of the Omnipod HCL were investigated in children aged 2–5.9 years with T1D with results presented at the 2019 ADA scientific meeting. The study included a 48–72-h HCL phase in a supervised setting. The study results showed overall lower mean glucose levels with closed loop as well as lower overnight values. Overall, time in range as well as percentage of hypoglycemia were significantly better with closed loop.[63]

Twelve families in the United Kingdom were surveyed to determine their perspectives and concerns regarding closed-loop technology for overnight use in very young children.[64] Nighttime was noted as the most challenging time for achieving glycemic control. All parents responded positively to the possibility of treating their children with closed-loop technology, and none were worried about making decisions regarding insulin delivery based on computer algorithms.

The many recent studies of very young patients with T1D show the importance of closed loop in this unique population and the unique challenges due to lower predictability of activities and meals, which make implementing closed-loop technology for this age group even more important.

CONCLUSIONS
T1D involves every aspect of daily life. In very young children, who cannot always articulate what they need or how they feel, the management of such a chronic disease is a burden on parents, siblings, and other caretakers. Improved and novel technologies in insulin delivery and glucose monitoring aim to enhance the flexibility of care and optimize glycemic control while trying to enable a "normal" life. Further studies are warranted in this specific age group owing to their unique physiological and behavioral characteristics.

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