The Impact of Technology on Current Diabetes Management

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**KEYWORDS**
- Technology
- Type 1 diabetes mellitus
- Children
- Adolescents
- Insulin analogues
- Insulin pump
- Continuous glucose monitoring
- Artificial pancreas

**KEY POINTS**
- Rapid-acting insulin analogues are more convenient to use than regular insulin. Long-acting analogues decrease nocturnal hypoglycemia. Insulin analogues are more expensive than regular and neutral protamine Hagedorn insulin.
- Compared with multiple daily injections, insulin pump therapy is associated with a modest improvement in glycemic control and may be associated with decreased frequency of severe hypoglycemia; available evidence suggests that quality of life is improved and the rate of pump discontinuation is low.
- Continuous glucose monitoring can improve glycemic control in children without increased hypoglycemia. The sensor-augmented insulin pump with low glucose suspension reduces rates of severe hypoglycemia and nocturnal hypoglycemia. Although technological innovations can improve diabetes outcomes and quality of life, maintenance of optimal glycemic control continues to be largely dependent on patient and family motivation, competence, and adherence to daily diabetes care requirements.
- The effective translation of technological advances into clinical practice is costly and requires a substantial investment in education of both practitioners and patients/families.
- Closed-loop “artificial pancreas” systems are currently in development and show great promise to automate insulin delivery with minimal patient intervention.

**INTRODUCTION**

In the past 2 decades, technological innovations have revolutionized the treatment of type 1 diabetes (T1D). Most recently, new insulin analogues and continuous glucose monitoring have been introduced to improve glycemic control and reduce the frequency of hypoglycemia. Insulin pumps, continuously-monitored glucose sensors, and artificial pancreas systems have all contributed to advancements in diabetes care. However, these technological advances come with challenges related to education, costs, and patient adherence. The implementation of these technologies into clinical practice requires a multidisciplinary approach involving patients, families, healthcare providers, and diabetes educators. The effective translation of technological innovations into improved outcomes for children and adolescents with diabetes is essential for their long-term health and quality of life.
monitors (CGM) have become available to complement improvements in glucose meters, insulin pumps, and pen delivery systems. In clinical trials, these technological advances have been shown to improve clinical outcomes; however, their effective translation into clinical practice is both costly and requires substantial investment in education of both practitioners and patients/families, and has had only a modest impact on clinical outcomes. For example, only 25% of youth with T1D enrolled in the Type 1 Diabetes Exchange Clinic registry in the United States meet the International Society of Pediatric and Adolescent Diabetes hemoglobin A1c (HbA1c) target of less than 7.5%.1

The aphorism “A tool is only as good as the person using it” is true for management of T1D in children and adolescents. Advances in technology offer potential opportunities to improve diabetes outcomes; however, successful intensive diabetes management continues to be driven by the competence of the patient/family and their motivation to devote the considerable time and effort required to maintain blood glucose (BG) levels in the near-normal range. Excellent glycemic control is largely contingent on specific self-management behaviors, including, but not limited to, frequent self-monitoring of BG (SMBG) levels, administering insulin before meals, and not missing insulin boluses.2

This article focuses on recent technological innovations; however, it is important to appreciate that technology has the potential to improve diabetes outcomes only when the fundamental requirements of effective self-care are firmly in place. Motivated and empowered patients require extensive diabetes self-management education and support to achieve the glycemic goals of intensive diabetes treatment.

NEW INSULINS

After the introduction of insulin in 1922, management of T1D consisted of injections of regular insulin before main meals and an additional injection in the middle of the night; however, after intermediate-acting and long-acting insulins were developed, most patients were treated with only 1 or 2 injections daily. In 1993, the Diabetes Control and Complications Trial (DCCT) showed that maintenance of near-normal glycemia with intensive diabetes therapy reduces the risk of microvascular complications3 and was the major impetus to develop better insulins, insulin-delivery systems, and insulin-replacement strategies that enable patients to more closely mimic physiologic insulin secretion.

Basal-bolus regimens with multiple daily insulin injections (MDI) or continuous subcutaneous (SC) insulin infusion (CSII, insulin pump), referred to as intensive insulin therapy, aim to mimic normal insulin production, which has 2 principal components: (1) basal insulin secretion suppresses lipolysis and balances hepatic glucose production with glucose utilization, and (2) prandial insulin secretion inhibits hepatic glucose production and stimulates glucose disposal after eating. The ability to simulate endogenous insulin production via SC insulin administration is limited by 2 factors: (1) inability to precisely reproduce the 2 distinct phases of prandial insulin release (a rapid first-phase followed by a more prolonged second-phase), and (2) insulin delivery into the systemic and not into the portal circulation.4

In the 1980s, human regular (soluble) insulin produced by recombinant DNA technology was introduced into clinical practice and rapidly replaced animal source insulins. Regular insulin is a short-acting prandial insulin, but its rate of entry into the circulation is too slow to match the absorption of glucose, and it remains in the circulation between meals, imparting a substantial basal component (Table 1). This mismatch leads to postprandial hyperglycemia unless injected at least 30 to
Neutral protamine Hagedorn (NPH) or isophane insulin is a suspension that had been widely used to provide the basal component of insulin regimens. Its inconsistent absorption and action profile results in highly variable intraindividual and interindividual pharmacodynamic effects (see Table 1) requiring patients to eat snacks between meals to prevent hypoglycemia. When given before dinner or at bedtime, NPH has an unphysiological and undesirable peak action overnight that is associated with a considerable risk of nocturnal hypoglycemia. Because of these characteristics of regular and NPH insulins, the timing and content of meals and snacks must be consistent from day-to-day, and it is challenging to meticulously balance insulin replacement with diet and exercise and achieve optimal glycemic targets without postprandial hyperglycemia, interprandial hypoglycemia, and excessive weight gain in patients with severe insulin deficiency. Insulin analogues were developed in an attempt to overcome these limitations of human regular and NPH insulins and afford patients greater lifestyle flexibility.

The first rapid-acting analogue (RAA), insulin lispro, was introduced in the mid-1990s, and subsequently 2 additional RAAs (insulin aspart and insulin glulisine) and 3 long-acting analogues (LAAs), insulin glargine, insulin detemir, and insulin degludec, have entered the clinical arena as alternatives to regular and NPH insulin, respectively (see Table 1). Insulin degludec is still in clinical trials in pediatrics and is not discussed further. Despite their considerably greater cost (see Table 1), worldwide use of insulin analogues has increased enormously, and analogues are the first and virtually the only choice for treatment of T1D in children and adolescents in many pediatric diabetes centers. Data from the T1D Exchange Clinic registry indicate that 98.6% of the 9919 participants younger than 18 years are exclusively using insulin analogues (T. Riddelsworth, PhD, written communication, 2014). A frequently asked question is: “Do their putative benefits justify their higher cost?”

### Table 1

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset of Action</th>
<th>Peak Action</th>
<th>Effective Duration</th>
<th>Retail Price per 10 mL Vial US$</th>
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<tbody>
<tr>
<td>Regular (soluble)</td>
<td>30–60 min</td>
<td>2–3 h</td>
<td>5–8 h</td>
<td>121–125</td>
</tr>
<tr>
<td>Lispro b</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>4–6 h</td>
<td>221</td>
</tr>
<tr>
<td>Aspart b</td>
<td>10–20 min</td>
<td>60–180 min</td>
<td>3–5 h</td>
<td>232</td>
</tr>
<tr>
<td>Glulisine</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>4–6 h</td>
<td>191</td>
</tr>
<tr>
<td>NPH or isophane</td>
<td>2–4 h</td>
<td>4–10 h</td>
<td>12–16 h</td>
<td>121–124</td>
</tr>
<tr>
<td>Glargine</td>
<td>2–4 h</td>
<td>No peak</td>
<td>20–24 h</td>
<td>278</td>
</tr>
<tr>
<td>Detemir</td>
<td>2–3 h</td>
<td>No peak</td>
<td>16–24 h</td>
<td>279</td>
</tr>
</tbody>
</table>

Abbreviation: NPH, neutral protamine Hagedorn.

a Source: [http://www.goodrx.com/](http://www.goodrx.com/) (accessed July 13, 2014); estimated retail cash price of commonly used insulins at a major national pharmacy chain operating in the vicinity of the authors’ institution. Also available as 3-mL (300-unit) cartridges for use in nondisposable insulin pens and as 3-mL (300-unit) prefilled disposable pens. Cost per unit of rapid-acting analogue in prefilled disposable pens is approximately 25% more than vials, whereas the cost per unit of long-acting analogues in prefilled disposable pens is approximately 5%–8% less than vials.

b According to manufacturers’ data; equivalent pharmacodynamic effects. Serum insulin profiles are usually based on an SC injection of 0.1 to 0.2 unit per kilogram of body weight; large variations may be observed within and between individuals, and smaller doses typically have a shorter duration of effect.

60 minutes before a meal and increases the risk of hypoglycemia between meals unless snacks are consumed.
RAPID-ACTING ANALOGUES

Compared with regular insulin, RAAs exist as monomers that are rapidly absorbed from SC tissue, resulting in a faster onset and shorter duration of action and, unlike regular insulin, their time to peak action is independent of dose.4,9–11 Intraindividual and interindividual absorption of RAAs are also less variable than regular insulin.12 For these reasons, they have been recommended as first-line prandial or bolus insulins. RAAs should be administered approximately 15 to 20 minutes before meals to match glucose absorption and limit postprandial glucose excursions.13,14 This is a major practical advantage compared with regular insulin, which should be injected at least 30 minutes before a meal.15,16

In special circumstances (eg, very young children, sick day management, gastroparesis), RAAs may be administered after eating to safely manage unpredictable food intake and absorption.13,17,18 It is important to note, however, that a bolus of RAA injected either with a syringe or an insulin pump approximately 15 to 20 minutes before starting a meal results in considerably better postprandial glucose control than when the insulin bolus is given immediately before or 20 minutes after meal initiation.19

Although the RAAs are modified human insulins with different chemical properties, their pharmacodynamic profiles (see Table 1) are not significantly different.20–22 In children and adolescents with T1D using a basal-bolus regimen (with glargine or NPH), insulin glulisine is comparable to insulin aspart both in terms of efficacy and safety23; and an industry-sponsored study comparing insulin aspart with insulin lispro (both delivered with a pump) showed comparable glycemic efficacy and frequency of hypoglycemia.24

Although short-term studies show that they reduce postprandial glucose excursions, several meta-analyses show no significant difference in glycemic control as measured by HbA1c when RAAs are compared with regular insulin in children and adolescents (Table 2).25–28 Furthermore, in an analysis of observational data representing “real life” collected over 12 years from 275 German and Austrian centers (37,206 children and adolescents 0–20 years) registered in the Diabetes Patienten Verlaufsdocumentation (DPV) database (corrected for age, center, and diabetes duration), HbA1c was statistically significantly lower in patients using regular insulin as compared with RAAs, 8.18% versus 8.32%, respectively.8

Compared with regular insulin, RAAs in combination with either NPH or ultralente as the basal insulin are associated with a significant reduction (3.1% vs 4.4%) in the occurrence of severe hypoglycemia in adults,29 including patients with a history of recurrent severe hypoglycemia.30 However, no such difference in the frequency of severe hypoglycemia has been shown in children or adolescents.25–27 Insulin lispro in combination with NPH has been associated with a decreased frequency of symptomatic or biochemical hypoglycemia and nocturnal hypoglycemia in adolescents,31 but not in prepubertal children. Furthermore, in a 26-week study of preschool children, comparing basal-bolus MDI therapy with mealtime insulin aspart or human regular insulin (both with basal NPH insulin), or CSII with insulin aspart, metabolic control parameters remained unchanged and equivalent (see Table 2).32

In open-label studies in adults, RAAs have been associated with modest improvements in quality of life (QOL) attributable to the convenience of more flexible regimens and the shorter interval between insulin administration and food consumption25,33; however, a randomized controlled trial (RCT) in adults with T1D did not show a significant improvement in QOL with RAAs.34 There are no comparable QOL data for children and adolescents. Nonetheless, treatment flexibility related to convenience with respect to the timing of administration is an important consideration that should not be underestimated.
LONG-ACTING INSULINS

In contrast to NPH, the LAAs are relatively peakless and have more reproducible pharmacodynamic profiles.35,36 Although dose-dependent, their duration of action is longer than that of NPH, and in some patients once-daily administration can achieve satisfactory 24-hour basal coverage. The duration of action of insulin detemir is shorter than that of glargine (see Table 1),37 and many patients with severe insulin deficiency require 2 injections of detemir daily to provide stable 24-hour basal coverage. One industry-sponsored study has shown that insulin detemir has a more reproducible pharmacokinetic profile (less variable absorption) than glargine in children and adolescents with T1D.38

Some observational studies have reported HbA1c improvements of 0.5% to 1.0% with LAAs compared with NPH,39–41 whereas others have shown no significant difference.42–46 Meta-analyses show that LAAs are associated with modest (~0.1%) or no reduction in HbA1c when compared with NPH insulin (see Table 2).27,28 In the large observational DPV database, HbA1c was significantly lower, 8.09% versus 8.4%, in patients treated with NPH compared with LAAs, respectively.8

LAAs do not reduce the risk of severe hypoglycemia in children and adolescents, but insulin detemir, in particular, is associated with decreased occurrence of nocturnal hypoglycemia (and less weight gain).27,28,47 A recent multinational RCT again showed that HbA1c levels were similar in preschool-age children and in older children and adolescents when insulin detemir, as compared with NPH (both in combination with

<table>
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<th>Table 2</th>
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<td>Meta-analyses of randomized controlled trials examining the effect of insulin analogues on HbA1c and hypoglycemia in children and adolescents with type 1 diabetes mellitus</td>
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<tr>
<td>Rapid-acting analogues</td>
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<td>Long-acting analogues</td>
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Comparisons are between rapid-acting insulin analogues (insulin lispro and insulin aspart) and regular human insulin and between long-acting analogues (insulin glargine and insulin detemir) and neutral protamine Hagedorn.

Statistically significant advantages associated with analogues are generally less than clinically important minimal differences, and advantages with respect to hypoglycemia are not consistent across comparisons.

a The overall rate of hypoglycemic episodes per patient per month did not differ significantly in prepubertal children. In adolescents, the event rate of overall hypoglycemia per patient per month was significantly reduced with insulin analogue.25

b Insulin lispro.
c Insulin aspart.
d Adolescents but not children.
e Insulin glargine.
f Insulin detemir.

LONG-ACTING INSULINS

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mealtime insulin aspart), was used for basal-bolus treatment. However, there was less weight gain and a lower risk of hypoglycemia with insulin detemir, attributed to its peakless and more consistent pharmacologic profile.48,49

Insulin glargine may cause a sensation of stinging or pain at the injection site. Careful analyses have concluded that glargine is safe, and concerns about its mitogenic and carcinogenic potential are unfounded.50

Cost-effectiveness analyses performed in adults show widely varying incremental cost-effectiveness ratios; however, no such analyses have been specifically performed in pediatric T1D.28

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

CSII, or insulin pump therapy, was introduced to treat T1D in the late 1970s and became widely used in pediatric practice only after publication of the DCCT results in 1993.51 In 1996, fewer than 5% of patients who started CSII were younger than 20 years. Over the intervening years, there has been a dramatic increase in the number of children and adolescents using pump therapy52; in the Type 1 Diabetes Exchange, representing 67 clinics in the United States, 55% of 13,316 participants younger than 20 years with T1D for more than 1 year were using an insulin pump.1 Successful use of CSII requires patients and families to receive intensive self-management education and ongoing support from an experienced diabetes team.

CSII mimics the normal pattern of insulin secretion, providing a continuous basal insulin infusion with superimposed boluses for food or correction of hyperglycemia. A major advantage of CSII is the ability to program changes in basal rates (eg, increase the basal rate from 4 AM to 9 AM to combat the dawn phenomenon or, conversely, decrease the infusion rate or temporarily suspend insulin infusion for physical exercise). In addition, pumps precisely calculate bolus doses and provide the option to extend bolus delivery over a variable time period to account for delayed digestion and nutrient absorption (eg, a meal such as pizza rich in protein and fat). Table 3 details the technological features of insulin pumps.

| Table 3
Technological features of insulin pumps

| Insulin delivery | • Low basal rates (0.025–0.05 units/h)
| | • Multiple different basal rates
| | • Temporary basal rates and basal suspension
| | • Small bolus increments (0.025–0.10 units)
| | • Extended boluses for delayed digestion
| | • Bolus calculator (based on BG level and carbohydrate quantity)
| | • Multiple insulin: carbohydrate ratios, sensitivity factors, BG targets
| | • Missed meal bolus reminder

| Safety features | • Alarms for occlusion and low insulin reservoir
| | • Active insulin calculation (prevents insulin stacking)
| | • Keypad lock (useful for toddlers)
| | • Waterproof or watertight

| Interface with BG monitoring | • Electronic logbook software
| | • Reminder alarms for BG checks, bolus doses
| | • Wireless communication with remote BG meter
| | • Integration with continuous glucose monitoring technology

Abbreviation: BG, blood glucose.

Adapted from Mehta SN, Wolfsdorf JI. Contemporary management of patients with type 1 diabetes. Endocrinol Metab Clin North Am 2010;39(3):584; with permission.
Insulin pump systems include the pump itself, a disposable reservoir for insulin, and an infusion set (consisting of a tube that connects the reservoir with a cannula inserted into the SC tissue). A disposable, tubeless patch pump also has been approved for use in children. Infusion sets and patch pumps are changed every 2 to 3 days. The average list price of an insulin pump is approximately $6500 for individuals without insurance and a typical warranty lasts approximately 4 years. The actual price varies depending on the brand and unique features of the pump. Related pump supplies typically cost approximately $1500 to $2000 per year. The patch pump has a lower initial cost, but a comparable total cost over the course of the warranty period.

Impact of Continuous Subcutaneous Insulin Infusion on Glycemic Control

Multiple pediatric studies have reported decreases in HbA1c with CSII; however, many of these studies are limited by small sample sizes, observational or retrospective design, short duration, or lack of control groups. A meta-analysis of observational and interventional pediatric and adult studies showed a 0.6% improvement in HbA1c with CSII compared with MDI therapy.53 A systematic review and meta-analysis of 6 short-term RCTs comparing CSII with MDI exclusively in children (165 participants) showed a statistically significant reduction in HbA1c with CSII (~0.24%), and there were no differences in the incidence of diabetic ketoacidosis (DKA) or severe hypoglycemia events.54 A recent prospective 7-year follow-up study of 345 pediatric patients using CSII in Australia showed that mean HbA1c was 0.6% lower in the pump cohort compared with controls (matched for age, duration of diabetes, and baseline HbA1c) who injected insulin.55

Impact of Continuous Subcutaneous Insulin Infusion on the Frequency of Acute Complications

Because RAAs are typically used in CSII, any interruption in basal insulin delivery rapidly leads to metabolic decompensation. To reduce this risk, BG levels must be measured at least 4 to 6 times daily. Early observational studies suggested an increased risk of DKA in pediatric patients using CSII56; however, in the recent aforementioned prospective Australian analysis, the rate of hospitalization for DKA was 50% lower (2.3 vs 4.7 per 100 patient-years).55 The decreased rate of DKA is probably a result of focused patient education and greater patient and family awareness of the consequences of interrupted insulin delivery with CSII.

RCTs in adults have shown decreased rates of severe hypoglycemia with CSII compared with MDI,57 but pediatric data are inconsistent. Pediatric observational studies have shown a decrease in the rate of severe hypoglycemia in patients using CSII55,58; however, the short-term pediatric RCT data in children have not shown significant differences in the occurrence of severe hypoglycemia between CSII and MDI (see Ref.52 for a detailed review), which may be attributable to the infrequency of severe hypoglycemia events and the lack of statistical power of small studies.

Impact of Continuous Subcutaneous Insulin Infusion on Quality of Life

Studies examining the psychosocial impact of CSII in children and adolescents have shown conflicting results. Several studies have documented improvement in children’s QOL or decreased parental anxiety with use of CSII.59–61 A recent German prospective multicenter study reported significantly increased QOL scores in preschool, school-age, and adolescent patients with T1D after using CSII for 6 months.62 Other studies, however, have shown no difference in QOL after initiating CSII.63,64 Inconsistent results and conclusions among these QOL studies may be ascribed to differences in methods and survey instruments in the various studies, as well as age differences in
the samples. Methods using qualitative analysis or open-ended questions may yield different results; for instance, describing their experiences in qualitative interviews, parents of young children with T1D reported that switching from MDI to CSII offered more freedom, flexibility around mealtimes, and spontaneity in their lives, as well as decreased worry. It is also noteworthy that the reported rates of discontinuation of pump therapy is low, ranging from 11% and 18% in single-clinic reports to 4% (463 of 11,710) in the large multicenter DPV database in Germany and Austria. These observations have been interpreted as suggesting that pump therapy improves patient satisfaction and quality life.

A systematic review and economic evaluation published in 2010 concluded that based on the totality of evidence, using observational studies to supplement the limited data from RCTs comparing CSII with optimal MDI in T1D, CSII provides some advantages over MDI (Box 1). The benefits were estimated to come at an extra cost of approximately £1700 (or approximately US$3000) per annum.

CONTINUOUS MONITORING SYSTEMS AND CLOSED-LOOP THERAPY

Real-time CGM devices measure glucose in the interstitial fluid every 5 minutes for up to 7 days via a short, thin subcutaneous probe (glucose sensor). There is a several-minute lag between plasma and interstitial glucose concentrations. SMBG values are still needed to calibrate CGM devices and to confirm glucose levels before an insulin bolus is administered or to confirm hypoglycemia before treatment. At this time, CGM devices cannot substitute for SMBG, but are valuable in providing detailed information on BG trends in the intervals between SMBG values, especially after meals and overnight.

A number of recent studies have assessed the impact of CGM on glycemic control in T1D. In the Juvenile Diabetes Research Foundation (JDRF)-sponsored study of CGM, an RCT comparing CGM with conventional SMBG in T1D subjects 8 years or older, adults who used CGM had a greater reduction in HbA1c with no increase in hypoglycemia. Although a clear benefit was not seen in the overall pediatric cohort (likely because of less frequent CGM use), more children (8–14 years) using CGM achieved a statistically significant HbA1c reduction compared with those using SMBG alone.

<p>| Box 1 |</p>
<table>
<thead>
<tr>
<th>Potential advantages of continuous subcutaneous insulin infusion compared with multiple daily injections</th>
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<tbody>
<tr>
<td>• Better blood glucose control as reflected by hemoglobin A1c</td>
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<tr>
<td>• Reduced glycemic variability</td>
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<tr>
<td>• Ability to combat dawn phenomenon</td>
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<tr>
<td>• Ability to decrease or suspend insulin infusion for physical exercise</td>
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<tr>
<td>• Reduced hypoglycemia</td>
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<td>• Improved quality of life</td>
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<td>o Reduced fear of hypoglycemia</td>
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<td>o Greater lifestyle flexibility</td>
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<tr>
<td>• Benefits for parents</td>
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<td>• Lower total daily insulin dose</td>
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Note that this result was not observed in adolescents older than 14 years. In another RCT (the Sensor-Augmented Pump Therapy for A1C Reduction 3 [STAR3] study), sensor-augmented insulin pump (SAP) therapy showed significant improvement in HbA1c levels in both adults and children (7–18 years) compared with a regimen of MDI and conventional SMBG; again, children were more likely to reach HbA1c targets than adolescents. In both of these trials, despite perceived value on the part of patients and parents, the frequency of CGM use decreased during the study period. Other studies also have shown that near-daily CGM use improves HbA1c levels. The data are less clear on the value of CGM alone in reducing the frequency of hypoglycemia in children and adolescents. In the JDRF and STAR3 trials described previously, rates of severe hypoglycemia were low and did not differ between CGM and non-CGM pediatric groups; however, these analyses were limited by very small numbers of severe hypoglycemia events.

In the STAR3 study, QOL analyses showed no significant differences in overall health-related QOL between SAP and MDI arms. However, caregivers in the SAP group had significantly improved scores on a survey measuring maladaptive behaviors around hypoglycemia prevention (eg, overtreating hypoglycemia or inappropriately reducing insulin delivery). In addition, key treatment satisfaction measures improved more in the SAP group.

It is noteworthy that despite the potential benefits of CGM, most pediatric patients with T1D are not using this technology. In a recent analysis of 17,317 patients younger than 26 years in the Type 1 Diabetes Exchange, 6% of children younger than 13 years, 4% of adolescents 13 to younger than 18 years, and 6% of young adults 18 to younger than 26 years had used CGM during the previous 30 days. Patients and families report barriers to CGM use, including insertion pain, alarm fatigue, accuracy issues, and skin irritation. Another major drawback is cost; in addition to the cost of the consumables (sensors and transmitters), the cost of a CGM receiver itself is typically $1000 or more. Health insurance plan coverage of CGM systems is variable.

Overcoming the barriers that prevent use of CGM data in daily T1D management is challenging. Irrespective of cost considerations, improvement in CGM devices and strategies for patient and family support are needed to increase the acceptability of CGM devices for long-term use in more youth with T1D.

**Sensor-Augmented Pump Therapy with Low Glucose Insulin Suspension**

New insulin pump systems offer automatic suspension of insulin delivery for up to 2 hours when a preset CGM glucose threshold is reached. This is an important advance toward automation of insulin delivery in patients with T1D, and studies have demonstrated a reduction in severe hypoglycemia and nocturnal hypoglycemia. In a recent 6-month RCT comparing insulin pumps only and automated insulin suspension in 95 children and adults with impaired hypoglycemia awareness, the combined rate of severe and moderate hypoglycemia was significantly reduced in subjects using automated insulin suspension (adjusted incidence rate 9.5 vs 34.2 per 100 patient-months). In an RCT of 45 patients with T1D ages 15 to 45 years studied in their homes, a predictive algorithm was used to suspend insulin delivery before hypoglycemia occurred. Participants had significantly fewer nights (21% vs 33%) with at least 1 sensor value of 60 mg/dL or lower on intervention (predictive algorithm) nights compared with control nights, without an associated risk of morning ketosis.

**Closed-Loop Insulin-Delivery Systems**

Closed-loop systems, also referred to as an “artificial pancreas,” feature continuous glucose sensing and automated insulin delivery with minimal patient intervention. Early
studies of closed-loop systems have shown great promise. In an RCT in adults, overnight closed-loop insulin delivery improved glucose control and reduced hypoglycemia, even after a large carbohydrate meal with alcohol. In a multinational trial comparing a closed-loop system with SAP therapy in children ages 10 to 18 years at a diabetes camp, subjects using closed-loop had better overnight glycemic control with less nocturnal hypoglycemia. Likewise, even in children younger than 7 years, closed-loop insulin delivery in a hospital study decreased the severity of overnight hyperglycemia without increasing hypoglycemia. Finally, recent trials show near-normal glucose levels in adults with T1D using a bihormonal (insulin and glucagon) closed-loop system. This system was recently also evaluated in adolescents (12–21 years) in a summer camp crossover study. In the adolescent population, comparing a 5-day closed-loop period to a control period, the mean plasma glucose was lower, 138 versus 157 mg/dL, but the percentage of time with a low plasma glucose reading was similar during the 2 periods. In sum, closed-loop systems improve the safety and efficacy of insulin therapy. Additional studies are in progress to refine closed-loop algorithms and further evaluate their performance in pediatric patients in the home setting.

SUMMARY

Several prospective observational studies show that over the past 2 decades, HbA1c levels have significantly improved and, equally important, rates of severe hypoglycemia have simultaneously decreased in pediatric T1D. Moreover, rates of microvascular complications have improved over this period. It is noteworthy, however, that in a study of more than 30,000 children and adolescents with T1D, published in 2012, the average HbA1c level was not different between treatment regimens, suggesting that the improvement in HbA1c cannot be completely explained by changes in the mode of insulin treatment per se (ie, increased use of MDI and CSII). It seems likely that improved health outcomes are largely attributable to widespread adoption and implementation of the principles of intensive diabetes management, including multidisciplinary team care, intensive patient education and self-management training, establishment of treatment goals, and more frequent SMBG to guide optimal insulin-dose selection. A critical review of the empiric data suggests that use of more physiologic insulin-replacement regimens with MDI and pumps, increased use of insulin analogues, and, most recently, use of CGM have contributed only modestly to lower HbA1c levels.

It is appropriate to ask why diabetes care providers so enthusiastically embrace new and expensive technologies when the “real-life” advantage of each is relatively small. The answer to this question is complex. One possible explanation includes the impact of marketing on health care providers and directly to patients and the influence of thought leaders (investigators) who conduct clinical trials under ideal conditions on selected, motivated patients. In addition, although QOL analyses in pediatric patients with T1D using pumps and CGM have yielded inconsistent results, providers may receive positive feedback from patients and families regarding “lifestyle” benefits of these technologies that serves to reinforce their prescribing patterns. However, many pediatric diabetes clinics do not have sufficient personnel resources required to optimally educate and train patients and families in intensive diabetes management using pumps and CGM, which requires a considerable and ongoing investment of time in patient education and support.

Looking ahead, the pace of current research suggests that within the next several years, “artificial pancreas” systems may become available that will reduce the burden
of care and enable children with T1D to maintain near-normal glycemia, especially overnight, with minimal risk of severe hypoglycemia. Meanwhile, as Skinner and Cameron have eloquently stated, it is important not to allow pharmacologic and technological considerations to subvert the critically important elements of comprehensive pediatric diabetes care, which include setting appropriate individualized treatment goals, a cohesive multidisciplinary diabetes team that shares a common philosophy of care, and psychosocial support.98

REFERENCES


