REVIEW

Insulin pump therapy in youths with Type 1 diabetes: uptake and outcomes in the 'real world'

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Practice Points

- Insulin pump use in youths with Type 1 diabetes is increasing steadily, especially in jurisdictions that provide universal funding for the cost of the pump and related supplies.
- Discontinuation rates are low and are related to patient factors, such as older age, female sex and higher hemoglobin A1c at 12 months after pump start.
- In cross-sectional studies, glycemic control is similar in patients using insulin pumps compared with injections. Many longitudinal studies show an improvement in hemoglobin A1c within the first year of starting pump therapy; however, it appears that hemoglobin A1c increases back toward baseline thereafter.
- Results on the impact of pump therapy on the rate of hypoglycemia are mixed.
- Overall, the rate of diabetic ketoacidosis (DKA) does not appear to be increased in patients using pump therapy; however, most episodes of DKA occur within the first year of pump use, suggesting a need for interventions targeting initial pump education and clinical support systems.
- Potential advantages of pump therapy must be balanced against the potential burden of increased cost and the risk of DKA in individual patients.
- In order to study the impact of patient, center and jurisdictional-level factors on diabetes-related outcomes for youths with Type 1 diabetes using insulin pumps, there is a need for high-quality data collected systematically at a population level.
- The failure to demonstrate significant advantages of pump therapy should not condemn this approach to treatment, but rather serve as an impetus to improve our understanding of how best to apply this technology, and to redouble our efforts to develop a closed-loop system.

SUMMARY A critical review of the literature about insulin pump therapy for youths with Type 1 diabetes in 'real-world' settings was performed. MEDLINE and EMBASE databases were searched for English language papers published between 2006 and August 2011 using terms for Type 1 diabetes, diabetic ketoacidosis, insulin pumps and children. We identified 263 papers and 22 met our inclusion criteria. There is an increasing proportion of youths with Type 1 diabetes using pumps and discontinuation rates are low. Glycemic control tends to

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improve in the first year of pump therapy but then increases back toward baseline. Evidence of the rate of diabetic ketoacidosis and hypoglycemia in pump therapy compared with insulin injections is mixed. If it occurs, diabetic ketoacidosis is most likely to occur within the first year of pump therapy.

Current management for individuals with Type 1 diabetes (T1D) is largely informed by the results of the Diabetes Control and Complications Trial (DCCT), a randomized controlled trial, and the Epidemiology of Diabetes Interventions and Complications, the long-term monitoring of subjects recruited into the DCCT. The DCCT demonstrated unequivocally that onset and/or progression of the long-term micro- and macro-vascular complications of diabetes could be reduced by approximately 50% by providing intensive insulin therapy through multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (insulin pump) [1,2]. Although these data were derived from individuals 13–39 years of age at recruitment into the study, the findings have been extrapolated to all individuals with T1D, a reasonable assumption in the younger age group too, where natural history studies show that the onset of early diabetic nephropathy, for example, is related to preceding glycemic control [3].

While adults with diabetes generally accept MDI regimens, their acceptability and success in pediatrics has historically been lower [4]. The direct cost of intensive therapy provided by insulin pump in children is estimated to be twice that required for MDI, depending on the local costs and practices [5]. A systematic review and meta-analysis of randomized controlled trials comparing pump to MDI in a total of 165 children with T1D found a modest improvement (0.24%) in hemoglobin A1c (HbA1c) in favor of pump therapy [6]. Such evidence was used to support a combined statement by the European Society for Paediatric Endocrinology, the Pediatric Endocrine Society and the International Society for Pediatric and Adolescent Diabetes recommending insulin pump therapy as an alternative to MDI for specific clinical indications and when appropriate support personnel are available [7].

The incremental costs of pump therapy meant that, until recently, its use was primarily restricted to those who could pay for it independently and those with private insurance. Responding to public and professional interest in the insulin pump's potential for optimizing glucose control and improving quality of life, some government programs have started to provide funding to cover the cost of pump therapy for youths with T1D [8].

Increased use of the pump may lead to widespread benefit; however, it may also have the potential for harm. For example, diabetic ketoacidosis (DKA) can arise in just 5 h if the pump's continuous insulin infusion is interrupted [9]. Furthermore, it may also add to the cost of healthcare without clear benefit. Existing evidence of efficacy has been generated in controlled settings with ideal support systems that may not accurately reflect the general pediatric population with T1D under 'real-world' conditions.

Differences in uptake and outcomes of insulin pump use in children and adolescents between countries and within countries may be related to funding arrangements, eligibility criteria for initiating and discontinuing pump therapy, center resources and healthcare provider attitudes and expertise. Furthermore, given the increased demand for pump training and clinical follow-up, the quality and thoroughness of the education and additional supports that families need to facilitate effective utilization may be different compared with when it was provided for fewer and more highly selected patients.

Objective

To determine the uptake, discontinuation, safety and effectiveness of insulin pump therapy for youths with T1D in real-world settings.

Methods

For our MEDLINE search, we used a combination of MeSH and free text terms for (diabetes mellitus, Type 1/ or diabetic ketoacidosis/) AND Insulin Infusion Systems/ AND All child (0–18 years) AND English AND 2006 to present. We used a combination of EMBASE descriptor and free text terms for (insulin dependent diabetes mellitus/ or diabetic ketoacidosis/) AND (infusion pump/ or infusion system/) AND (limit to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) or ((infan* or child* or teen* or adolescent* or

pediatric* or paediatric*).mp.)) AND 2006 to present. The reference lists of all included studies were also reviewed to identify any relevant publications.

Eligibility criteria were:

- Studies had to include individuals under the age of 18 years;
- Subjects with a diagnosis of T1D treated with an insulin pump;
- Nonexperimental studies in real-world settings.

Studies were excluded if participants were pregnant or had non-T1D. Outcomes assessed were pump uptake, discontinuation, glycemic control, hypoglycemia and/or DKA. Studies were categorized by study population as either population-based or clinic-based and also on the basis of availability of funding to cover the cost of the pump. The quality of each report was assessed by identifying study limitations and potential sources of bias.

Results

The search strategy for MEDLINE without Revisions <1996 to August Week 4 2011> retrieved 247 references, of which 246 were unique and not duplicated in our other searches. The search strategy for EMBASE <1980 to 2011 Week 34> retrieved 32 references, of which 17 were unique and not duplicated in our other searches. We identified 18 studies from our search that met inclusion criteria. Four additional studies were identified from the reference lists of included studies [10–13]. The characteristics of included studies are described in **Table 1**.

Eight of the 22 included studies are population-based [10,11,14–19] and the remaining 14 are clinic-based [12,13,20–31]. Nine studies are set in the USA, where pump funding would largely be dependent on insurance coverage, but some state governments do cover the cost of insulin pumps for low-income individuals who qualify for Medicaid [10,16,20,21,24,27,28,30,31]. See **Table 2** for a summary of the funding arrangements for insulin pumps in children and youths in jurisdictions studied in the included papers.

Study quality

The majority of included papers use cross-sectional or paired studies designs, therefore, it is difficult to rate their quality using a validated scale or score. We have attempted to identify the limitations and potential sources of bias in the included studies in **Table 3**.

Pump uptake

Eight of the included studies report pump uptake **(Table 4)** [10,17,19,22,23,28–30].

Pump uptake reported in studies set in jurisdictions that provide universal funding for the cost of the pump, ranges from 11.0 to 30% [17,19,22,23,29] compared with 14–62.9% in studies set in jurisdictions that do not universally fund the cost of the pump [10,28,30]. Not all jurisdictions that provide universal funding cover the full cost of pump therapy. The study with the highest rate of uptake, 62.9%, is set in a clinic-based population where there is no universal funding for the cost of the pump and the mean household income is above the state and national averages [28].

In the US studies, pump use is associated with higher household income, being Caucasian, having private healthcare insurance and higher parental education [10,28,30]. Pump use has increased over time in jurisdictions that provide universal funding [17,19,29]. In one population-based study from France, there is no significant relationship between uptake and academic affiliation or the size of the center; however, there is variability in uptake between centers ranging from 1.3 to 53% [19].

Discontinuation

Six studies report on pump discontinuation rates and they range from 3.2 to 18% **(Table 5)** [13,18,21,23,27,31]. Older age [13,18,21,31], female sex [13,18,21,31], more advanced pubertal status [21,31], higher HbA1c at pump initiation [13], higher HbA1c at 12 months after pump start [21,27,31], lower frequency of blood glucose monitoring [31], single-parent family [31] and a higher rate of severe hypoglycemia (SH) in the first year of pump use [31] are factors that were found to be associated with discontinuation. Discontinuation rates do not appear to be related to whether there is universal funding or not: 7.2–18% [21,27,31] in jurisdictions that do not provide universal funding for the cost of the pump and 3.2–11.3% [13,18,23] in those that do.

Glycemic control

Six population-based studies [10,11,14,15,17,18] and 11 clinic-based studies [12,20,22–28,30,31] report on glycemic control **(Table 6)**.

Table 1. Characteristics of studies included in review of uptake, discontinuation and outcomes of pediatric insulin pump therapy in 'real-world' settings.

Study (year)	Year of study	Number of patients studied	Age of patients (years)	Region of study	Source of study population	Data source	Outcomes measured	Ref.
Berghaeuser *et al.* (2008)	1992–August 2007	343	3.18 (0.4–16.67)	Germany and Austria	63 centers <18 years, started pump therapy within 4 weeks of T1D diagnosis	Computerized database	DKA Hypoglycemia HbA1c	[15]
Cope *et al.* (2008)	1996–2005	1594 events reported	Not reported	USA	All youths aged 12–21 years	Adverse event reports from database	Adverse events (hypoglycemia, DKA and death)	[16]
Danne *et al.* (2008)	2004–2005	1086	11.9 ± 4.2	Europe and Israel	30 centers Patients <19 years with T1D using an insulin pump	Chart review and pump download	Glycemic control Hypoglycemia DKA	[14]
De Vries *et al.* (2011)	2000–2008	530	15.2 ± 6.3	Israel	Single center, all patients starting pump therapy	Chart review	Discontinuation	[13]
Hanas *et al.* (2009)	1999–2000	115 patients with DKA	Pump users 14.9 ± 2.2	Sweden	Children with DKA on pumps	Questionnaire	Uptake Glycemic control DKA	[17]
Hofer *et al.* (2010)	1995–2009	11,710 adults and children on pumps (71% <19 years)	19.2 years	Germany and Austria	All pump users among the participating centers in the electronic diabetes database	Electronic diabetes database	Discontinuation Glycemic control	[18]
Kapellen *et al.* (2007)	December 2005	4612 (1567 analyzed)	12.4 ± 4.1	Germany and Austria	Children and adolescents with documented indications for pump therapy at 128 pediatric diabetes centers	Electronic diabetes database	Uptake Hypoglycemia Glycemic control	[11]
Paris *et al.* (2009)	2001–30 October 2007	2743 with T1D (22% on pump)	14.0 (4.2) (age at visit)	USA	Six centers Children <20 years at DM diagnosis	Survey, healthcare provider reports, chart review	Uptake Glycemic control Hypoglycemia ED visits Hospitalizations	[10]
Sulmont *et al.* (2011)	2001 and 2007	9073	Not reported	France	Hospital departments involved in pediatric or adolescent diabetes management	National survey	Uptake	[19]
Babar *et al.* (2009)	July 1999–June 2003	46	9.1 ± 3.4	USA	Single pediatric center, all youth starting pump therapy	Chart review	Discontinuation	[21]
Goss (2010)	November 2008–30 June 2009	17	10.8 (4–18)	Australia	Recipients of 'donor pumps' at one pediatric diabetes center	Chart review	Uptake Glycemic control	[22]

DKA: Diabetic ketoacidosis; DM: Diabetes mellitus; ED: Emergency department; MDI: Multiple daily injections; T1D: Type 1 diabetes.

Table 1. Characteristics of studies included in review of uptake, discontinuation and outcomes of pediatric insulin pump therapy in 'real-world' settings (cont.).

Study (year)	Year of study	Number of patients studied	Age of patients (years)	Region of study	Source of study population	Data source	Outcomes measured	Ref.
Hanas and Adolfsson (2006)	1993–1999	27	15.6 ± 3.7	Sweden	Duration of T1D ≥2 years	Chart review	Uptake Discontinuation Hypoglycemia DKA	[23]
McVean *et al.* (2007)	Not reported	236	14.5 ± 3.9	USA	Patients aged 2–22 years with T1D for ≥1 year using pump therapy for ≥6 months	Review of medical records	Glycemic control	[24]
Nimri *et al.* (2006)	January 1998–September 2003	23 prepubertal 127 adolescents	Prepubertal median 5.4 (1.6–8.6) Adolescent median 13.7 (9–17)	Israel	Single center Patients with T1D on MDI for at least 12 months prior to pump start and who used a pump for at least 12 months	Medical records	Glycemic control Severe hypoglycemia DKA	[25]
Pinhas-Hamiel *et al.* (2010)	June 1996–May 2007	113	13.8 ± 6.1 (mean age at pump initiation)	Israel	Single center Patients with T1D followed by two physicians	Medical records	Glycemic control	[26]
Scrimgeour *et al.* (2007)	September 1997–September 2005	291	13.3 ± 3.7 (age at pump initiation)	USA	Single center Patients with T1D on pump therapy for at least 1 year and data available for 1 year prior to pump initiation	Chart review	Discontinuation Glycemic control Severe hypoglycemia DKA	[27]
Springer *et al.* (2006)	January–September 2003	455 youths with T1D 62.9% on pumps	11.8 ± 3.9 (all youths with T1D)	USA	Single center All youth <18 years with T1D	Clinical database	Uptake Glycemic control	[28]
Sulli and Shashaj (2006)	1998–2000	42	12.2 ± 3.4	Italy	Single center All patients starting pump with data available for 12 months prior to pump start	Chart review and prospective clinical and laboratory data collection	Glycemic control Severe hypoglycemia DKA	[12]
Tonella *et al.* (2010)	1 October 2007–31 January 2008	152 youths with T1D 18 on pumps	Not reported	Switzerland	Outpatient clinic of a university children's hospital	Clinical and demographic data collected at a clinic visit and previously collected study data	Uptake Severe hypoglycemia Glycemic control	[29]
Wilkinson *et al.* (2010)	Not reported	150 youths on pumps	13.6	USA	Single center Diagnosis of T1D for at least 1 year, pump use for at least 6 months, downloadable pump, aged 5–20 years	Data from pump download and electronic medical record	Glycemic control	[20]

DKA: Diabetic ketoacidosis; DM: Diabetes mellitus; ED: Emergency department; MDI: Multiple daily injections; T1D: Type 1 diabetes.

Table 1. Characteristics of studies included in review of uptake, discontinuation and outcomes of pediatric insulin pump therapy in 'real-world' settings (cont.).

Study (year)	Year of study	Number of patients studied	Age of patients (years)	Region of study	Source of study population	Data source	Outcomes measured	Ref.
Wintergerst *et al.* (2010)	2008	701 with T1D 98 (14%) on pumps	13.5 (4.3) all youths with T1D	USA	Single center, review of all records for youths with T1D for >6 months	Medical records	Uptake Glycemic control	[30]
Wood *et al.* (2006)	1 January 1998–31 December 2001	161 on pumps	14.1 ± 3.7 (mean age at pump start)	USA	Single center, all youths beginning pump therapy during study period	Medical chart review and electronic laboratory system	Discontinuation Glycemic control Severe hypoglycemia	[31]

DKA: Diabetic ketoacidosis; DM: Diabetes mellitus; ED: Emergency department; MDI: Multiple daily injections; T1D: Type 1 diabetes.

The mean HbA1c of youths on pumps reported in cross-sectional population studies was 8.0% in two studies [10,14], and 7.2–8.4% in clinic-based studies [10,14,20,22,28,30]. Eight studies found that HbA1c improves within the first year after pump start [11,12,22,23,25–27]. However, of those that followed patients for more than 1 year, three studies found that HbA1c increases after the first year of pump therapy [12,23,26], while two found a sustained improvement in HbA1c over time [25,27]. In youths starting on insulin pumps within 4 weeks of diagnosis of T1D, there is no significant difference in HbA1c between those on pumps compared with MDI 1 year after pump start [15].

The range of mean HbA1c levels reported by studies set in a jurisdiction that provides funding for the cost of pumps is no different from those in which there is none: 7.6–8.0% [14,22] and 7.2–8.4% [10,20,28,30], respectively.

Factors found to be associated with poorer glycemic control are older age [10,14,22,24,25], longer duration of T1D [24,25] and higher baseline HbA1c [24]. Two studies report that those with higher baseline HbA1c levels have the biggest improvement in HbA1c on the pump [23,25].

■ Diabetic ketoacidosis

Five population-based studies [10,14–17] and four clinic-based studies [12,23,25,27] report the rate of DKA. The rate of DKA in studies ranges from 0 to 22 episodes per 100 patient-years [10,12,14,15,17,23,25,27]. In two studies, the rate of DKA is higher after pump start, compared with before pump start [25,27] and in two other studies, it is higher in those on pumps compared with those on insulin injections [15,17]. The number of episodes of DKA was found to be highest within the first year of pump use [12,17].

By contrast, one study reports a lower rate of DKA in patients on insulin pumps compared with injections [15] and another reports that, after adjusting for confounding factors, those who used a pump were less likely to be hospitalized compared with those on injections [10]. HbA1c was found to be higher in those with DKA in one study [14] and lower in another [17]. The range of the rate of DKA is 0–22 episodes per 100 patient-years in jurisdictions that provide funding for the cost of pump [12,14,15,17,23,25] compared with 3.98 episodes per 100 patient-years in one study set in a jurisdiction that does not fund the cost of the pump [27].

■ Hypoglycemia

The rate of hypoglycemia associated with seizure or loss of consciousness in patients on the pump ranges from 0 to 7.96 events per 100 patient-years [11,12,14,15,27]. There is a significant reduction in the rate after pump start in some studies [11,27] and no change in the rate after pump start in others [10,12]. The rate of hypoglycemia in the first year after pump start was found to be higher in patients who eventually discontinued pump therapy compared with those who continued [31]. Of the studies set in jurisdictions that universally fund the cost of the pump and report the rate of hypoglycemia before and after pump start, one reports a reduction in the rate of hypoglycemia [11] and the other reports no reduction in the rate of hypoglycemia [12].

The rate of hypoglycemia requiring assistance from another person ranges from 5–16 episodes per 100 patient-years [15,23]. In patients that started pump therapy because of severe hypoglycemia (SH; requiring help from another person), the rate of SH fell from 52.1 to 24.8/100 patient-years [11]. SH causing unconsciousness or convulsions is associated with a higher insulin dose in one study [14].

Discussion

■ Uptake

The US studies vary in their estimates of uptake. A population-based US study reports that 22% of youths with T1D are using pump therapy [10], while one clinic-based study reports that 62.9% use pumps [28] and the other reports 14% [30]. All three studies agree that pump therapy use is associated with higher household income, being Caucasian, having private healthcare insurance and higher parental education [10,28,30]. In a clinic-based study in the USA, having private healthcare insurance and higher frequency of blood glucose monitoring was found to be significantly correlated with insulin pump use among adolescents with T1D [32]. Therefore, discrepancy in uptake between US studies is likely to be a reflection of the characteristics of the patient population and the practice patterns of healthcare professionals.

Physician recommendation to initiate pump therapy is probably also influenced by clinical guidelines, as well as by family preferences and physician attitudes [33]. Differences in uptake between and within countries, regardless of the model of pump funding, may be related to the overall organization of diabetes care, eligibility

Table 2. Funding arrangements for pediatric insulin pumps.

Country	Funding arrangement
Germany and Austria	Reimbursement is available [41]
USA	Private only. Medicaid covers low income people in some states
Australia	Since 2008, children <18 years old with Type 1 diabetes and no private health insurance have been eligible to receive coverage from the Australian government and the Juvenile Diabetes Research Foundation for up to 80% of the total purchase price of an insulin pump based on financial need [101]
France	Nationwide pump reimbursement since 2000 [19]
Sweden	Pumps and pump accessories have been reimbursed since 1997 [23]
Israel	Patients are reimbursed equally by the health insurance agencies for all costs of the pump [13]
Italy	Full reimbursement since the 2000s [41]
Switzerland	Reimbursement is available [41]

criteria for starting pump therapy and center resources and expertise.

In jurisdictions where there is either partial or full universal funding for pumps, these factors are also likely to influence patterns of uptake. The socioeconomic status (SES) and parental education level of patients using pumps may differ compared with those not using pumps, despite both groups being eligible to receive partial or full universal government funding. Even in the context of universal funding, uptake varies widely between jurisdictions and between centers within jurisdictions [19,22]. Although there is discussion about the role of supportive healthcare services in determining uptake, there are no consistent findings about what specific factors may explain the disparities. Studies have found no significant association between academic affiliation, center size or model of care and the rate of pediatric insulin pump uptake [19,34].

There has been an increase in pediatric pump use over time in jurisdictions that provide universal funding [17,19,29]. In the Province of Ontario (Canada), there are approximately 8000 children and youths with diabetes. In 2010, approximately 3000 youths with T1D were enrolled in a government-funded insulin pump program. Therefore, we estimate that between 35 and 40% of youths with T1D in Ontario are using an insulin pump. The proportion of youths using insulin pumps in Ontario may be higher than the current proportion of youths in other jurisdictions because Ontario provides 100% universal funding, compared with some others that provide only partial funding. SES and parental education of youths on pumps in Ontario may be slightly more diverse compared with other populations in which the cost of pump therapy is only partially or not universally funded. However, there are still likely to be differences in these patient level factors between those using pumps compared with those on injections within Ontario. There is a gap in knowledge about the characteristics and diabetes-related outcomes of youths using insulin pumps in the real world that merits further investigation.

■ Discontinuation

Discontinuation rates of insulin pump therapy among youths with T1D in real-world settings are low. The range of discontinuation rates reported in studies set in jurisdictions that differ in their funding arrangement for insulin pumps overlap. Because these studies include heterogeneous patient populations, one would have to account for the patient-level factors found to be associated with higher rates of discontinuation (see results section) in order to comment about the effect of the funding arrangement for pumps on discontinuation rates. It is unlikely that the model of insulin pump funding alone significantly affects the patient-level characteristics of pump users within a jurisdiction, although future study is required to confirm this hypothesis. Other center-level and physician-level factors, such as eligibility criteria, the availability of 24 h clinical support and physician attitudes and beliefs about pump therapy, probably play an important role in the selection of patients who initiate and discontinue insulin pumps.

A study set in Austria, a country that universally funds the cost of pumps, explored the reasons for discontinuation of pump therapy. This qualitative study included physicians who prescribe pump therapy in children and youths,

Table 3. Study design and limitations.

Study (year)	Study design	Study limitations	Ref.
Berghaeuser *et al.* (2008)	Observational cohort	Relatively short follow-up period (12 months), potential ascertainment bias in measuring episodes of hypoglycemia and mild DKA	[15]
Cope *et al.* (2008)	Cross-sectional	Accuracy of event reporting uncertain, cannot determine causality, lack of detail about patient factors, cannot determine the incident rate of events	[16]
Danne *et al.* (2008)	Cross-sectional	Lack of a standardized approach to pump therapy between centers, analysis is limited by availability of data from the electronic database	[14]
De Vries *et al.* (2011)	Case–control	Single center, could not measure quality of life and parental involvement owing to retrospective nature	[13]
Hanas *et al.* (2009)	Cross-sectional	Concern about the reliability of the retrospective questionnaire data, missing data from some centers in 1 year of data collection could potentially lead to bias; however, the rate of DKA in each year was similar so this missing data is unlikely to affect the conclusions	[17]
Hofer *et al.* (2010)	Observational cohort	Lack of a standardized approach to pump therapy between centers, data elements are limited by what is available from the electronic database: unable to measure reasons for discontinuation	[18]
Kapellen *et al.* (2007)	Observational cohort	Lack of a standardized approach to pump therapy between centers	[11]
Paris *et al.* (2009)	Cross-sectional	Just less than 50% of registered children completed the study protocol, older and African–American youths were less likely to participate, uncertain if insulin regimens of participants and nonparticipants are similar, could not examine factors associated with the choice of provider and their impact on choice of insulin regimen and outcomes, potential error in the self-reported frequency of insulin administration and blood glucose testing, could not assess the relationship between provider type, insulin regimen and outcomes	[10]
Sulmont *et al.* (2011)	Cross-sectional	No information available about the decision-making criteria for pump initiation at each center, not able to take into account individual patient factors, such as age, duration of diabetes and socioeconomic status, that may influence pump use	[19]
Babar *et al.* (2009)	Retrospective observational cohort	Single center, concern about external validity since patients on pump therapy were highly selected, data availability limited to what is available from the chart, small sample size	[21]
Goss (2010)	Retrospective paired study	Small sample size in a single center, concern about external validity of results	[22]
Hanas and Adolfsson (2006)	Cross-sectional	Single center, small sample size, did not adjust for age and duration of diabetes in the analysis of HbA1c, frequency of clinic visits was different for pump users compared with those on injections, possibility of missed episodes of mild DKA or hypoglycemia if diabetes center not notified	[23]
McVean *et al.* (2007)	Case–control	Retrospective, data limited to what is available from the chart, single center	[24]
Nimri *et al.* (2006)	Retrospective paired study	Single tertiary center, concern about external validity, possible missed episodes of mild DKA or hypoglycemia if not reported to diabetes team	[25]
Pinhas-Hamiel *et al.* (2010)	Retrospective paired study	Number of patients decreased over time, long-term outcomes were determined with a relatively small number of patients, additional confounders, such as psychosocial factors, economic status, education and family status, that may affect outcome were not included	[26]

DKA: Diabetic ketoacidosis; HbA1c: Hemoglobin A1c.

Table 3. Study design and limitations (cont.).

Study	Study design	Study limitations	Ref.
Scrimgeour *et al.* (2007)	Retrospective paired study	Single center, concern about external validity since center criteria for pump start may differ from others, did not assess quality of life	[27]
Springer *et al.* (2006)	Cross-sectional	Single center, fewer African–American or Hispanic children in the upper income strata, other important factors, such as psychosocial factors and family and school support, were not measured	[28]
Sulli and Shashaj (2006)	Retrospective paired study	Single center, small sample size, limited external validity due to center-specific selection criteria for pump therapy that included elevated HbA1c, possible missed episodes of hypoglycemia and mild DKA since these were patient-reported	[12]
Tonella *et al.* (2010)	Cross-sectional	Single center, measured severe hypoglycemia only	[29]
Wilkinson *et al.* (2010)	Cross-sectional and prospective paired study	Potentially biased sample of the population using pumps since data only available for some patients, did not measure other potentially important factors, such as psychosocial factors and school and family support	[20]
Wintergerst *et al.* (2010)	Retrospective observational cohort	Single center, did not measure other important factors, such as psychosocial factors and school and family support, did not measure provider prescribing practices	[30]
Wood *et al.* (2006)	Observational cohort	Single center, did not measure other important factors, such as psychosocial factors and school and family support	[31]

DKA: Diabetic ketoacidosis; HbA1c: Hemoglobin A1c.

and found that when pump discontinuation was requested by the patient, it was mostly owing to nonmedical reasons, while if it was physician initiated, it was because the patient was not compliant or that clinical values had deteriorated [22]. In the same study, patients with T1D who were former pump users reported issues related to the catheter and social/psychological factors (such as visibility and the pump feeling like a foreign body) as reasons for discontinuing pump therapy. Technical problems with the pump or worsening glycemic control were not reported by patients to be important factors in the decision to stop pump therapy. Other physician-level and diabetes center-level factors may also be important in the selection of patients for insulin pumps. These factors were not consistently reported in the included studies, and therefore we cannot comment on the influence of these on discontinuation rates. There is a lack of evidence about the effect of eligibility criteria and other center-level factors, such as the availability of 24-h clinical support on the rate of pump discontinuation. Modifiable factors identified in our study that were associated with discontinuation are higher HbA1c at 12 months after pump start, lower frequency of blood glucose monitoring and a higher rate of SH in the first year of pump use. These may be important risk factors to identify in pump users so that interventions can be planned in order to reduce the future rate of pump discontinuation.

■ Glycemic control

The range of mean HbA1c of youths on insulin pumps in studies in this review (7.2–8.4%) is similar to that of a large population-based sample of youths with T1D on all insulin regimens reported in a study from the Hvidøre Study Group (8.2 ± 1.4%) [35]. This study is an observational, multicenter, cross-sectional study involving 21 pediatric diabetes centers from 19 countries in 2005. The Hvidøre data suggest that in the real world, glycemic control is similar in those using insulin pumps and injections. Although overall improvement in glycemic control is not observed, it does not appear that glycemic control deteriorates among pump users.

In the two studies that found a sustained improvement of HbA1c over time, there were a decreasing number of patients followed over time [25,27]. Nimri and colleagues report that HbA1c levels continued to improve over the first 3 years after pump start. They present data for 279 patients at 1 year after pump start, but for only 81 patients at 3 years after pump start [25]. Similarly, Scrimgeour and colleagues report improvements in the change in HbA1c levels from 1 year prior to pump start at yearly intervals until 8 years after pump start. They report

Table 4. Summary of findings from studies that report insulin pump uptake in youths with Type 1 diabetes in a review of 21 studies.

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Population-based				
Hanas *et al.* (2009)	In 1999, 7.4% used pumps In 2000, 11.0% used pumps	Not reported	–	[17]
Paris *et al.* (2009)	22% used pumps	Older age, non-Hispanic white, higher household income, higher parental education, private insurance, female	Range across centers was 12.7–32.2% Range across provider type was 12.6–31.8%	[10]
Sulmont *et al.* (2011)	16% used pumps Frequency of pump use at each center: 1.3–53%	No difference in size or academic affiliation	There was a tenfold increase in the number of pediatric patients using pumps from 2001 to 2007 In pediatric centers, 38% of pumps were started in the year before this study	[19]
Clinic-based				
Goss (2010)	In one pediatric center 46 patients use pumps (25% of the local children with T1D). Of the 46, 17 use 'donor pumps'	Not reported	–	[22]
Hanas and Adolfsson (2006)	27 out of 89 (30%) of all patients with T1D followed at one center use pumps	Not reported	–	[23]
Springer *et al.* (2006)	62.9% used pumps	Median income was higher in the pump-treated group Fewer African–American and Hispanic children used pumps compared with Caucasian children	–	[28]
Tonella *et al.* (2010)	11.9% used pumps in 2008 compared with 0% in 1998	Not reported	Very few toddlers use pump therapy (one aged 2–3 years and one aged 4–5 years). All other children on pumps were 10 years or older	[29]
Wintergerst *et al.* (2010)	100 (14%) used pumps	Of those with public insurance, 4% used pumps Of those with private insurance, 19% used pumps	–	[30]

T1D: Type 1 diabetes.

data for 291 patients at 1 year after pump start, but for only 11 patients after the eighth year [27]. It is possible that those who were followed until the end of the study had better glycemic control compared with those who were lost to follow-up.

Having a higher baseline HbA1c has been associated with the biggest improvement in HbA1c on the pump [23,25]. However, having a higher baseline HbA1c is also associated with discontinuation [13]. An explanation for this finding may be that those with higher baseline HbA1c who continue pump therapy, are able to improve their glycemic control; however, there are probably many youths with a high baseline HbA1c who discontinue pump therapy as they continue to struggle with the management of their diabetes.

As more jurisdictions provide funding for the cost of the pump, the population characteristics of pump users may change to include a slightly wider range of SES. The extent to which this change will occur is probably related to whether or not the funding is universal, partial or full, and also on the criteria for pump eligibility and other center-level and physician-level factors. Whether these changes will affect treatment outcomes is unclear. Two Australian studies have examined glycemic control in government subsidized pump users. Thong and colleagues report that 10 months after starting pump therapy HbA1c levels fell significantly in the group

with private health insurance-funded pumps but not in the group with public hospital-funded pumps [36]. Another Australian study examining the outcomes of 17 youths with T1D who are using subsidized pumps found an improvement in HbA1c 10 months after pump start compared with the 12 months prior to pumps start [22]. Six of the 17 patients followed at this particular center received funding for their pumps as a result of grants and community fundraising and the remainder received government financial assistance that does not cover 100% of the cost of the pump [22]. This study population may have been more motivated and intensively supported by the diabetes healthcare team. Increased use of the pump by less motivated patients potentially increases the risk of missed boluses, the biggest barrier to optimum use of the pump [37].

■ Diabetic ketoacidosis

As the uptake of pediatric insulin pumps increases, it is important to consider the impact of increased use on the rate of DKA, a serious and potentially life-threatening complication. Results are mixed regarding the rate of DKA in pump users compared with those on insulin injections (see **Table 7**). Some studies found a rate of DKA in pump users that is higher than in those using insulin injections. One study found a trend toward a higher rate of DKA after pump start in the prepubertal group [25]. Furthermore, in two studies, the rate of DKA was higher within the first year after starting pump therapy [12,17]. This finding suggests that interventions targeting the education of patients starting pump therapy and/or the availability of clinical support for new pump patients may be able to reduce the risk of DKA in the period immediately after pump start.

Table 5. Summary of findings from studies that report the rate of insulin pump discontinuation in youths with Type 1 diabetes in a review of 21 studies.

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Population-based				
Hofer *et al.* (2010)	3.2% discontinued during the study period	60.5% were female Highest rate of discontinuation in 10–15 year olds (2%) Lowest discontinuation rate in <5 year olds (0.1%)	–	[18]
Clinic-based				
Babar *et al.* (2009)	15% discontinued over 4 years	Older age, female, puberty Higher HbA1c 12 months after pump start	Patients highly screened prior to pump start, good baseline glycemic control, highly motivated	[21]
De Vries *et al.* (2011)	11.3% discontinued 2.2% discontinued within 3 months	Older age, female, higher HbA1c at pump start	Pump discontinuation rates declined over time	[13]
Hanas and Adolfsson (2006)	Two patients (7.4%) discontinued pump use during the 5-year follow-up period	Not reported	These two patients who discontinued were not included in the 5-year follow-up study	[23]
Scrimgeour *et al.* (2007)	21 out of 291 (7.2%) discontinued pump therapy during the study period	Discontinued group: baseline HbA1c 8.9% ± 0.7 and was similar at the most recent value prior to discontinuation (8.9% ± 1.6). Both are higher than mean HbA1c for the cohort at the same time period	–	[27]
Wood *et al.* (2006)	29 patients (18%) discontinued pump therapy after an average of 3.8 ± 1.1 years of follow-up	Discontinued group: Female, older, more advanced pubertal status, less frequent blood glucose monitoring, from one-parent families, higher rate of severe hypoglycemia in the year following pump start, higher HbA1c at 1 year after pump start and at the most recent visit	Causes for discontinuation: Major problems (DKA, insulin omission): 28% Diabetes burnout: 28% Minor problems (infusion site issues): 21% Body image concerns associated with wearing the pump: 14% Weight gain: 10%	[31]

DKA: Diabetic ketoacidosis; HbA1c: Hemoglobin A1c.

Table 6. Summary of findings from studies that report glycemic control in youths with Type 1 diabetes using insulin pumps in a review of 21 studies.

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Population-based				
Berghaeuser *et al.* (2008)	HbA1c decreased after diagnosis in pump and MDI groups. No difference in HbA1c between groups at 1 year after pump start	Not reported	f/u period 1 year Study population restricted to those <5 years	[15]
Danne *et al.* (2008)	Mean HbA1c in study population 8.0% ± 1.3	Older age, longer duration of T1D and longer duration of pump use were associated with higher HbA1c	Eligibility criteria: pump with 90 days storage capacity compatible with uploading software	[14]
Hanas *et al.* (2009)	HbA1c at DKA admission: pump group: 9.1% ± 1.5 injection group: 10.8% ± 2.2	Not reported	–	[17]
Hofer *et al.* (2010)	Discontinued group: HbA1c at the end of pump treatment was worse (9.00% [SE ± 0.11]) compared with before (8.40% [SE ± 0.10])	HbA1c at end of pump therapy was higher in those aged 5–15 compared to in the younger and older age groups and in those who discontinued after at least 2 and 3 years	–	[18]
Kapellen *et al.* (2007)	HbA1c 8.1 ± 1.76% at pump start	HbA1c after 3 years of pump therapy by indication for pump therapy: dawn phenomenon (8.0%), reduction of hypoglycemia (8.1%), reduction of hyperglycmia (8.8%), flexibility for daily life (7.9%), motivation (8.4%), and failure of injection therapy (9.17%)	Patients who started pump therapy because of poor glycemic control and for other indications, HbA1c improved in the first year after pump start, but by 3 years increased to prepump levels	[11]
Paris *et al.* (2009)	Unadjusted HbA1c in pump group 8.0% (1.2) Adjusted HbA1c 9.0% (0.1) Adjusted for: sex, race, center, household income, parental education, insurance, age at visit, duration of T1D, fasting c-peptide and number of blood sugar checks per day	Higher frequency of self blood glucose monitoring associated with lower HbA1c independent of insulin regimen	Both unadjusted and adjusted HbA1c in pump group were lowest compared with all other insulin regimens	[10]
Clinic-based				
Goss (2010)	Prepump mean HbA1c was 9.2% (SD: 1.4) Postpump mean HbA1c was 7.6% (SD: 0.83) after mean pump duration of 10.2 months (SD: 6.1)	Younger patients (<12 years) had a significant reduction in HbA1c	–	[22]
Hanas and Adolfsson (2006)	HbA1c in pump compared with injections: HbA1c in pump users lower in the first (8.4% ± 1.2) and second years (8.3% ± 1.2) after start compared with the year prior to start (8.9% ± 1.3) HbA1c in years 3–5 post-start were not different compared with HbA1c before start	High HbA1c as an indication for pump therapy associated with lower HbA1c at 1, 2, and 3 years post-start compared with the year prior to start; however, in years 4 and 5, HbA1c was similar to those prior to start	–	[23]
McVean *et al.* (2007)	38% on pumps met their HbA1c goal HbA1c of group that met their goal: 6.9% ± 0.7 HbA1c of group that did not meet their goal: 8.6% ± 0.9	Patients who met their goal were younger, had a shorter duration of T1D, had lower baseline HbA1c levels, and had a higher number of catheter sites	The goal levels of HbA1c were not reported	[24]

DKA: Diabetic ketoacidosis; f/u: Follow-up; HbA1c: Hemoglobin A1c; MDI: Multiple daily injections; SD: Standard deviation; SE: Standard error; T1D: Type 1 diabetes.

Table 6. Summary of findings from studies that report glycemic control in youths with Type 1 diabetes using insulin pumps in a review of 21 studies (cont.).

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Clinic-based (cont.)				
Nimri *et al.* (2006)	Mean HbA1c during pump therapy was lower compared with HbA1c during MDI in the prepubertal and adolescent groups Prepubertal: at pump start 8.6% ± 1.2, 1 year after pump start 8.4% ± 0.8 Adolescents: at pump start 8.6% ± 1.3, 1 year after pump start 8.4% ± 1.5	There was a significant interaction between change in HbA1c and age and the duration of pump therapy for the first 3 years. There was a significant interaction between the baseline HbA1c level and change in HbA1c (-1.7% for baseline HbA1c ≥10% and 0.2% for baseline HbA1c ≤7%)	–	[25]
Pinhas-Hamiel *et al.* (2010)	Lowest mean HbA1c: 7.6% at the initial 3-month period after start HbA1c increased for all time periods after the initial 3-month period after start: 7.7% in the first 6 months 7.9% from 1 to ≤2 years 8.1% from 2 to ≤3 years and 3 to ≤4 years 8.3% from 5 to ≤7 years	HbA1c after start were independently associated with metabolic control before start and increased with time after start Sex did not have a significant effect Children aged 10 to ≤15 years had higher HbA1c Shorter duration of time from diagnosis to start was associated with better HbA1c after start	All patients in the clinic are offered pump therapy irrespective of baseline glycemic control Psychosocial factors, economic status, education and family status were not assessed	[26]
Scrimgeour *et al.* (2007)	HbA1c was lower (8.2% ± 0.9) at 1 year after start compared with baseline HbA1c (8.7% ± 1.0)	Those continuing pump therapy for ≥1year continued to show improvement in HbA1c from baseline for each year of analysis. Those who used pump therapy for ≥6 years showed the greatest improvement in HbA1c	The mean HbA1c in the clinic's nonpump patients at the start and end of the study period was 8.4 and 8.3%, respectively	[27]
Springer *et al.* (2006)	Pump therapy associated with lower HbA1c Pump group: HbA1c 7.2% Injection group: HbA1c 8.1%	Not reported	–	[28]
Sulli and Shashaj (2006)	HbA1c at start was 9.1 ± 1.5%	HbA1c during the first to fourth years after start was lower compared with HbA1c at start	–	[12]
Tonella *et al.* (2010)	HbA1c did not differ between insulin regimens. In 2008, the median and 25th/75th percentile HbA1c in all patients in the clinic was 7.6 (7.0/8.3) and in those on pumps it was 7.5 (6.8/8.2)	Duration of diabetes was associated with HbA1c, no other factors were associated with HbA1c	–	[29]
Wilkinson *et al.* (2010)	Mean HbA1c 8.4% (5.1–13.8%)	Younger group (5–10 years) had lower mean HbA1c (7.8%) compared with both the middle age (10–15 years; 8.6%) and the older age group (15–20 years; 8.6%)	–	[20]

DKA: Diabetic ketoacidosis; f/u: Follow-up; HbA1c: Hemoglobin A1c; MDI: Multiple daily injections; SD: Standard deviation; SE: Standard error; T1D: Type 1 diabetes.

Table 6. Summary of findings from studies that report glycemic control in youths with Type 1 diabetes using insulin pumps in a review of 21 studies (cont.).

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Clinic-based (cont.)				
Wintergerst *et al.* (2010)	Mean HbA1c for all on pump: 8.2% (1.4) Mean HbA1c for all patients with T1D: 9.0% (2.0)	No difference between mean HbA1c in pump group depending on insurance type Mean HbA1c for pump group with public insurance: 8.8% (1.3) Mean HbA1c for pump group with private insurance: 8.1% (1.4)	HbA1c lower in private versus public insurance (8.6% [1.7] vs 9.8% [2.2])	[30]
Wood *et al.* (2006)	Discontinued vs continued: Similar baseline HbA1c discontinued vs continued (8.5% ± 1.4 vs 8.4% ± 1.4) Discontinued had higher HbA1c at 1 year after start (8.6% ± 1.3 vs 8.0% ± 1.3) and at the most recent clinic visit (9.4% ± 2 vs 8.4% ± 1.2)	HbA1c at discontinuation was higher than at baseline Discontinued: average increase in HbA1c was higher in those who used pump therapy for >2.5 years compared with those who discontinued within 2.5 years (1.9 vs 0.3%)	–	[31]

DKA: Diabetic ketoacidosis; f/u: Follow-up; HbA1c: Hemoglobin A1c; MDI: Multiple daily injections; SD: Standard deviation; SE: Standard error; T1D: Type 1 diabetes.

The results in our study about differences in the rate of DKA in pump users depending on whether or not the cost of the pump is funded are mixed. We do not observe a higher rate of DKA in pump users in jurisdictions that fund the cost of the pump compared with those that do not. Like other outcomes, we need to identify the factors associated with DKA in youths using pumps and control for those, before we can assess the effect of the funding arrangement for pumps on the rate of DKA. However, there is a lack of data on the factors that predispose youths using insulin pumps to DKA in the real world. Only two studies report on the association of HbA1c with DKA in pump users and the results are conflicting [14,17].

Another concern is that, as universal funding for the cost of pumps becomes more widespread, the patient characteristics of youths using pumps may change to include a group that is less motivated and therefore may be at a higher risk for complications of T1D, including DKA [38,39]. Further studies are required to understand the evolving characteristics of youths using insulin pumps and diabetes-related outcomes.

■ Hypoglycemia

The impact of pump therapy in youths with T1D on the rate of hypoglycemia in real-world settings is mixed **(Table 8)**. None of the studies found an increase in the rate of hypoglycemia in those using insulin pumps, suggesting that for this outcome, insulin pump use in real-world settings is safe. However, the evidence does not show a reduction in the rate of hypoglycemia, a theoretical benefit of insulin pump therapy. Hypoglycemia is a difficult outcome to measure because most studies rely on self-reporting to identify episodes of hypoglycemia, and the definition of hypoglycemia differs between studies. The heterogeneity of study settings and designs, ascertainment of hypoglycemic events and the small number of hypoglycemic episodes reported makes it difficult to draw any generalized conclusions about this outcome. It is possible that individual characteristics (e.g., loss of early warning symptoms of hypoglycemia with lower HbA1c level) may lead to higher or lower risks of hypoglycemia.

Conclusion

Data from studies set in the real world suggest that there is an increasing proportion of youths

Table 7. Summary of findings from studies that report the rate of diabetic ketoacidosis in youths with Type 1 diabetes using insulin pumps in a review of 21 studies.

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Population-based				
Berghaeuser *et al.* (2008)	No episodes of DKA in study period MDI control group had 1.76 episodes per 100 patient-years	Not reported	f/u period 1 year study population restricted to those <5 years	[15]
Cope *et al.* (2008)	460 reports of DKA	Not reported	Adolescents only Almost all reports were from the manufacturer 6.4% of all reports for all complications identified adolescent-specific contributing factors including problems with education, noncompliance, and problems during sports or other activities	[16]
Danne *et al.* (2008)	Event rate of 6.26 per 100 patient-years	Higher HbA1c	Eligibility criteria for inclusion in study: pump with a 90-day storage capacity compatible with uploading software	[14]
Hanas *et al.* (2009)	DKA in pump users: 1999: 3.2 per 100 patient-years 2000: 3.6 per 100 patient-years Overall DKA incidence: 1999: 1.4 per 100 patient-years 2000: 1.7 per 100 patient-years	HbA1c at DKA admission: pump group: 9.1% ± 1.5 injection group: 10.8% ± 2.2	77% of episodes of DKA occurred within the first year of pump start	[17]
Paris *et al.* (2009)	3.2% had one or more hospitalizations	After adjusting for: sex, race, center, household income, parental education, insurance, age at visit, duration of T1D, fasting C-peptide, and number of blood sugar checks per day those who used a pump were less likely to be hospitalized compared with those on injections	Self-reports of hospital admission occurring during the 6 months before the study visit	[10]
Clinic-based				
Hanas and Adolfsson (2006)	No episodes of DKA in pump or injection patients during the cross-sectional study year, 1999. In the 5-year follow-up period, DKA occurred at a rate of 4.7 per 100 patient-years	Not reported	It is possible that there were missed episodes of DKA if they were treated at home	[23]
Nimri *et al.* (2006)	Prepubertal group: Prepump: 0 events per patient-year Postpump: 0.22 events per patient-year Adolescent group: (no significant difference) Prepump: 0.19 ± 0.74 events per patient-year Postpump: 0.17 ± 0.46 events per patient-year	Not reported	Most DKA events were due to technically interrupted insulin supply	[25]

DKA: Diabetic ketoacidosis; f/u: Follow-up; HbA1c: Hemoglobin A1c; MDI: Multiple daily injections; T1D: Type 1 diabetes.

Table 7. Summary of findings from studies that report the rate of diabetic ketoacidosis in youths with Type 1 diabetes using insulin pumps in a review of 21 studies (cont.).

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Clinic-based (cont.)				
Scrimgeour *et al.* (2007)	Prepump: 1.39 events per 100 patient-years Postpump: 3.98 events per 100 patient-years	Not reported	Episodes of DKA were reported by patients at each clinic visit and entered into the clinic's electronic database. Accuracy of the chart data was previously confirmed	[27]
Sulli and Shashaj (2006)	No difference in the rate of DKA during pump therapy compared with before. Episodes of DKA (episodes/patient-year): Year prior to pump start: 0.03 First year: 0.05, Second year: 0, Third year: 0.03, Fourth year: 0	Not reported	Two episodes in two patients occurred during the first year after starting pump therapy. These were among the first patients started on pump therapy at this center	[12]

DKA: Diabetic ketoacidosis; f/u: Follow-up; HbA1c: Hemoglobin A1c; MDI: Multiple daily injections; T1D: Type 1 diabetes.

with T1D using pump therapy. Overall, discontinuation rates are low and are related to some specific patient-level factors. Glycemic control reported in cross-sectional studies is similar in groups using insulin pumps compared with injections. HbA1c tends to improve in the first year after starting pump therapy and reverts toward baseline levels thereafter. With regards to acute complications of T1D, including DKA and hypoglycemia, the evidence is mixed. In general, there is no overwhelming evidence to suggest that the rate of hypoglycemia is different with insulin pump therapy. However, there are some reports of an increased frequency of DKA in pump users, especially within the first year after starting pump therapy. This finding is important since this adverse outcome is potentially preventable by identifying users at the highest risk for DKA and implementing interventions geared at initial pump education and ongoing clinical support.

It is difficult to assess the quality of real-world studies with the same rigor as randomized controlled trials; nonetheless, data from multicenter and population-based registries provide important evidence about the effectiveness of pediatric pump therapy because the results are likely to be externally valid. Although true for muticenter studies too, it is particularly important that single-center studies are interpreted in the context of the characteristics of the study population, the local funding arrangement for insulin pumps and the characteristics of the center providing care.

Based on available real-world evidence, the clinical benefits to pump therapy are not uniformly demonstrated, and it remains possible that the rate of DKA is higher among pump patients. There are differences in results among centers, and a better understanding of the bases of those differences might further clarify the pros and cons of pump therapy. Despite these uncertainties, there has been an increase in the use of insulin pump therapy for T1D in youths.

When considering pump therapy, potential advantages, such as increased flexibility in lifestyle and patient satisfaction, precision of insulin delivery and reduction of number of injections, must be balanced by potential risks of treatment, including DKA, deterioration of glycemic control due to missed boluses and skin damage and infection. Thus, there is a need to further explore the role of possible factors such as practice guidelines, industry pressure and

Table 8. Summary of findings from studies that report the rate of hypoglycemia in youths with Type 1 diabetes using insulin pumps in a review of 21 studies.

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Population-based				
Berghaeuser *et al.* (2008)	No episodes of hypoglycemia with seizures and loss of consciousness in patients on pumps. No difference in incidence of SH between quarters in pump group. Rate of SH in the first year after start: 5–15 episodes per 100 patient-years	Not reported	SH definition: requiring assistance from another person f/u period 1 year Study population restricted to <5 years and all were newly diagnosed	[15]
Cope *et al.* (2008)	167 reports of hypoglycemia	Not reported	Adolescents only Almost all reports from the manufacturer 6.4% of all reports for all complications identified adolescent-specific contributing factors	[16]
Danne *et al.* (2008)	Event rate of SH 6.63 per 100 patient-years	SH was associated with higher insulin dose No association with age, T1D duration, pump duration, HbA1c	SH definition: hypoglycemia causing unconsciousness or convulsions Eligibility criteria: pump with a 90-day storage capacity compatible with uploading software	[14]
Kapellen *et al.* (2007)	In group starting pump because of SH, rate of SH fell from 52.1 per 100 patient-years to 24.8 per 100 patient-years. No change in rate of hypoglycemic events with seizure or unconsciousness. Rates of hypoglycemia did not change in patients who started pump therapy for any other indication	Patients who started pump therapy because of SH were younger and had lower HbA1c than those starting pump therapy for another indication	SH definition: requiring help from another person	[11]
Paris *et al.* (2009)	Frequency of hypoglycemia was not different in the pump group compared with other insulin regimens 10.3% had one of more episodes of hypoglycemia	Not reported	Self-reports of SH (seizure, treatment with glucagon or needing outside assistance) occurring during the 6 months before the study visit	[10]
Clinic-based				
Hanas and Adolfsson (2006)	SH 16.0 per 100 patient-years in pump patients (four patients) SH 51.0 per 100 patient-years in patients on injections (ten patients)	Not reported	SH definition: needing help from another person or for young children not being able to eat without help	[23]
Nimri *et al.* (2006)	No SH in prepubertal group. Less SH during pump therapy in the adolescent group: Prepump: 36.5 events per 100 patient-years First year postpump: 11.1 events per 100 patient-years	Not reported	SH definition: any hypoglycemic event that required the assistance from another person or resulted in seizure or coma. SH recorded at clinic visits or if reported by telephone. Lack of hypoglycemia in the prepubertal patients may be due to the small sample size	[25]
Scrimgeour *et al.* (2007)	9.06 episodes per 100 patient-years of SH before start compared with 7.96 per 100 patient-years after start	Not reported	Episodes of SH reported by patients at clinic visits. SH definition: seizure or loss of consciousness. Accuracy of the chart data was previously confirmed	[27]

f/u: Follow-up; HbA1c: Hemoglobin A1c; SH: Severe hypoglycemia; T1D: Type 1 diabetes.

Table 8. Summary of findings from studies that report the rate of hypoglycemia in youths with Type 1 diabetes using insulin pumps in a review of 21 studies (cont.).

Study (year)	Findings	Factors associated with outcome	Other comments	Ref.
Clinic-based (cont.)				
Sulli and Shashaj (2006)	No difference in SH after start compared with before SH (episodes per 1000 patient-years): Year prior to pump start: 20.0 First year: 20.0 Second year: 20.0 Third year: 20.0 Fourth year: 0	Not reported	SH definition: loss of consciousness requiring intervention by other people with intramuscular and/or intravenous administration of glucagon or glucose. SH episodes were documented routinely at each follow-up visit	[12]
Tonella *et al.* (2010)	One episode of SH in the group on intensive regimen of insulin injections	Not reported	SH definition: blood glucose <3.5 mmol/l with loss of consciousness or seizure, severe symptoms of hypoglycemia disabling the child temporarily, requiring the assistance of another person to give something to eat or a glucagon injection	[29]
Wood *et al.* (2006)	1 year prior to pump therapy, similar rate of SH in discontinued versus continued groups (11.9 vs 23.0 events per 100 patient-years) Continued group: SH decreased from the year prior to start compared with the year after (23.0 vs 7.4 events per 100 patient-years) Discontinued group: SH was higher in the year after pump start compared with continued group (23.2 vs 7.4)	Not reported	SH definition: requiring assistance with parenteral or enteral therapy	[31]

f/u: Follow-up; HbA1c: Hemoglobin A1c; SH: Severe hypoglycemia; T1D: Type 1 diabetes.

the hope of 'closing the loop' that may influence healthcare providers to recommend pumps as best therapy or for families to request it. Healthcare systems must also assess the validity of these potential reasons for increased use while also assessing the increased costs associated with pump therapy.

The associations between center and jurisdictional-level factors, such as the model of care, pump training, availability of 24-h clinical support, eligibility criteria for initiating pump therapy on the one hand and uptake and outcomes on the other have not been investigated in population-based studies. It is highly likely that at least some of these factors differ between centers and influence pump uptake and outcomes. Pediatric insulin pump therapy is a 'complex intervention' [40] in healthcare involving the technology itself, financial arrangements that support its accessibility and the coordination of education and service delivery to ensure the initial education of youths and their caregivers, as well as ongoing support for insulin dose adjustment and troubleshooting pump problems. The uptake and success of this technology depends on the capacity of the system to provide adequate support for pediatric pump users beyond funding for the devices and related supplies.

Future perspective

Understanding how complex healthcare interventions, such as insulin pumps, are implemented into the structure of health service delivery for youths with T1D is important for informing strategies to improve outcomes of pediatric insulin pump therapy, but may also be applied to other current and emerging diabetes technologies, such as continuous glucose monitors and closed loop-systems.

In order to study the impact of center and jurisdictional-level factors on diabetes-related outcomes, there is a need for more high-quality population-level data. Collection of such data requires an investment in information technology infrastructure that allows the systematic collection of clinical and demographic data of all youths with T1D within a healthcare system. Access to such data would facilitate the development of studies designed to fill knowledge gaps about the factors that impact diabetes-related outcomes in youths with T1D and inform practice at both the clinical and policy level.

The failure to demonstrate significant advantages of pump therapy over MDI therapy in

children and youths with T1D should not condemn this approach to treatment, but rather serve as an impetus to improve our understanding of how best to apply this technology, and to redouble our efforts to develop a closed-loop system, which removes the vagaries of individual decision-making from the treatment regimen.

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