Review Article

20 Years of insulin lispro in pediatric type 1 diabetes: a review of available evidence

Kaiserman K, Jung H, Benabbad I, Karges B, Polak M, Rosilio M. 20 Years of insulin lispro in pediatric type 1 diabetes: a review of available evidence. Pediatric Diabetes 2017: 18: 81–94.

Background: Insulin lispro, the first rapid-acting insulin analog, was developed 20 years ago and has been studied in multiple situations and various populations.

Objective: To review the literature on the use of insulin lispro in children, adolescents, and young adults.

Patients: Children, adolescents, and young adults with type-1-diabetes.

Methods: One hundred and twenty-two relevant publications, identified by a systematic (MEDLINE) and manual literature search, were reviewed.

Results: Multiple daily injection (MDI) treatment with insulin lispro or other rapid-acting insulins, mainly using neutral protamine Hagedorn (NPH) insulin as the basal component, was associated with reduced postprandial glucose excursions, similar or improved HbA1c levels, and similar or reduced risks of severe hypoglycemia when compared with regular human insulin across all age-groups. Continuous subcutaneous insulin infusion (CSII)-treatment with insulin lispro also showed similar or improved glycemic control vs. MDI- or other CSII-regimens across all age-groups, without increasing the rate of severe hypoglycemia. The other two more recently developed rapid-acting insulins (aspart, glulisine) demonstrated non-inferiority to lispro on HbA1c. Long-term observational studies and real-life experience indicate that the increasing use of optimized MDI- and CSII-regimens with insulin lispro was associated with improvements in overall glycemic control.

Conclusions: For almost 20 years, rapid-acting insulins, in particular insulin lispro as the first-in-class, have contributed to broadening the treatment options for the unique needs of pediatric patients with type-1-diabetes across all age-groups, and have enabled more physiological insulin administration. Now widely used, they have allowed pediatric patients to safely reach better glycemic control, with more flexibility in their daily lives.

Insulin replacement should be as physiological as possible in patients with type 1 diabetes. This is of particular importance in pediatric patients, as they face a lifetime with the disease (1–3). In the Diabetes Control and Complications Trial (DCCT) (4) and in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study (5), the key learnings were that intensive insulin treatment with either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), together with patient support and education, provided better glycemic control compared with twice daily (BID) injections, and reduced the incidence of diabetes complications, such as retinopathy, in adults and adolescents with type 1 diabetes (6, 7). However, in the intensive therapy arm of the DCCT, adolescents had higher HbA1c values than adults (8.1% vs. 7.2%) (8), indicating that HbA1c targets for adults may be...
difficult to achieve in adolescents (7, 8). After 10 years of follow-up in the DCCT and EDIC studies, the average HbA1c had become similar in both treatment and age groups. In contrast to the adult group, the risk reduction benefit for progressive retinopathy was no longer present in the originally intensively treated adolescent group (8). In pediatric populations, optimal glycemic control without increasing the risk of hypoglycemia is not easy to achieve, but seems to be key for sustained reduction in microvascular complication risk (8), and may be important for normal brain development (9).

Given that intensive therapy in the DCCT was associated with better microvascular outcomes, and also with a higher rate of severe hypoglycemia, a key advance in insulin therapy has been the development of rapid-acting insulin analogs with a more physiological time/action profile to better control postprandial blood glucose (BG) excursions and reduce the risk of hypoglycemia (3, 10). The development of basal insulin analogs allowed further improvement of glycemic control when used in combination with rapid-acting insulins, and these regimens are now recommended by the guidelines (11).

Insulin lispro was the first rapid-acting insulin analog to be developed and has been available for clinical use since 1996 in adult and pediatric patients (12). Regulatory approval for use in pediatric patients of all age-groups was based on two pediatric randomized controlled trials (RCTs) (12–14). Its rapid absorption into the bloodstream enables administration closer to a snack or meal than regular human insulin, or potentially even immediately after eating (1, 10, 15–18). This flexibility is particularly beneficial in view of young children’s variable and sometimes unpredictable eating patterns. Rapid-acting insulins have been tested and used in pediatric patients with type 1 diabetes for two decades now, and are included in the treatment recommendations of the American Diabetes Association (ADA) (3) and International Society for Pediatric and Adolescent Diabetes (ISPAD) (2, 19) as an alternative to regular human insulin to optimize insulin regimens (10, 20).

This review describes and discusses the positive impact of insulin lispro in different insulin regimens (MDI, CSII) on the efficacy and safety of insulin treatment for various pediatric, adolescent, and young adult age groups, and provides an outlook on the potential future use of rapid-acting insulins.

Methods

Use of insulin lispro in children and adolescents (0–18 years) or young adults (19-25 years) with type 1 diabetes was reviewed, based on a prespecified literature search of the MEDLINE database via PubMed (detailed methods in Supporting Information Appendix S1 and Fig. S1). The reference lists of identified articles were manually searched for further relevant publications. In addition to data from the systematic search, newer publications were included post hoc during the writing process. Quality assessment of original research study publications was based on the respective study design – meta-analyses and RCTs of ≥4-week duration were considered most reliable (21). Important ‘real-world’ evidence was also added.

A large volume of data on the use of insulin lispro for type 1 diabetes is available. This review focuses on the efficacy and safety aspects of insulin lispro when used in different treatment regimens relevant for pediatric age-groups. The review aims to place published clinical trial data for insulin lispro into the context of more recent experiences and evidence from daily practice (‘real-world’ experience) with insulin lispro and rapid-acting insulins in general (as insulin lispro often is not differentiated from other rapid-acting insulins in reports of “real-world” data).

Results

The initial systematic MEDLINE search, based on prespecified search algorithms, yielded 160 hits, of which 82 publications were retained after the final full-text review (for details see Fig. S1). Manual checking of the references identified 22 additional MEDLINE-listed publications, resulting in a total of 104 clinical trials and review publications identified through the systematic approach. During the writing process, 41 additional MEDLINE-listed publications were identified manually and added post hoc, while 19 publications previously identified by the systematic approach were no longer used (outdated review manuscripts, publications on topics no longer addressed in the final manuscript), resulting in a total of 126 cited publications.

Pharmacokinetics and pharmacodynamics of insulin lispro and rapid-acting insulins in general

Insulin regimens based on short-acting (regular) and intermediate-acting neutral protamine Hagedorn (NPH) human insulins are limited in their ability to reproduce the physiological profile of endogenous insulin secretion (10, 15). Rapid-acting insulins have been developed to more closely mimic the physiological response of endogenous human insulin to food intake, to improve control of postprandial BG excursions, and to reduce the risk of hypoglycemia (15, 18, 22).

Three rapid-acting insulins are currently available for use in adult and pediatric patients: insulin lispro (indicated in all patients regardless of age), insulin aspart (in patients ≥2 years), and insulin glulisine (in
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rates were significantly reduced. Also, lispro compared with regular human insulin in CSII provided lower postprandial hyperglycemia and HbA1c levels, and similar or reduced incidence of hypoglycemic episodes in adults (37). Switching from MDI to CSII improved glycemic control, decreased the rate of severe hypoglycemia, and improved patient’s quality-of-life and treatment satisfaction (38, 39).

Efficacy and safety of insulin lispro in pediatric populations treated with MDI regimens

Insulin lispro bolus injections have been used as part of basal-bolus MDI regimens in 20 prospective clinical trials, in a total of 2829 children and adolescents/young adults with type 1 diabetes (13, 14, 33, 40–57) (Figure 1). These included 10 RCTs specifically evaluating insulin lispro in a total of 1300 patients (13, 14, 33, 40–46) (Table S1). In most of the earlier trials, insulin lispro was combined with NPH insulin, given CID in most cases. A few more recent trials have used long-acting insulin analogs such as glargine, given QD, as the basal component (38) (Fig. 1; details in Table S1). In the majority of RCTs, patients received three preprandial injections of insulin lispro per day, given within 15 min before each meal (Table S1), and insulin lispro made up 26–52% of the total daily insulin dose (13, 14, 33, 45, 48). Four additional non-RCTs and observational studies in more than 800 pediatric patients, including one observational study presenting subgroup analyses for patients aged 0–4.5–12, and 13–18 years (50), have specifically evaluated the switch of bolus insulin from regular human insulin to insulin lispro, while the basal insulin component, usually NPH insulin BID, was kept unchanged (50–53) (Fig. 1).

Glycemic control with MDI treatment. Blood glucose control. The main rationale for using rapid-acting insulins such as insulin lispro is to decrease postprandial BG excursions to achieve more physiological BG profiles (15). BG control was evaluated for preprandial insulin lispro injections as part of basal-bolus MDI regimens vs. regular human insulin in 1297 pediatric and adolescent patients (13, 14, 33, 40–46). At the end of the treatment periods (usually 3–4 months), mean 2 h postprandial BG levels were lower after injection of lispro when compared with regular human insulin for most time points and in the majority of studies, regardless of the age group assessed (Fig. 2 and Table S1).

In toddlers, it may be difficult to estimate the optimal insulin dose before meals, due to their variable appetite and carbohydrate consumption (15). Their rapid onset of action allows dosing of rapid-acting insulins just before or even immediately after meals (15).

Learnings from studies in adults

Large studies in adults provided a solid basis for the evaluation of insulin lispro in the pediatric population. Pediatric studies enrolled limited numbers of patients, had limited power, and were rather used as proof-of-concept studies for applicability in different age groups. A Cochrane meta-analysis from 2006 including 49 RCTs, 44 of them in adults, suggested that short-acting analogs such as insulin lispro were associated with an overall small decrease in HbA1c and mild hypoglycemia, and a major decrease in the risk of severe hypoglycemia, when compared with regular human insulin (34). In addition, studies in adults with type 1 diabetes comparing an MDI regimen of insulin lispro plus insulin glargine vs. an ‘all non-analog human insulin’ regimen (35) or vs. insulin lispro plus NPH insulin (36) have shown that HbA1c was significantly improved and hypoglycemia

patients ≥6 years) (10, 15, 16, 18, 22–24). Their reduced hexamer aggregation capacity, due to their modified molecular structure, enables them to be absorbed more rapidly into the bloodstream when compared with regular human insulin (15), and to be administered closer to a snack or meal (15).

From the first studies published on insulin lispro in the 1990s, it was clear that inversion of the proline and lysine amino acids at the C-terminal of the β-chain resulted in faster absorption after subcutaneous injection, relative to regular human insulin (15, 18, 25, 26). Hence, insulin lispro has an earlier onset of action (0–15 min vs. 30–45 min for regular human insulin), reaches peak blood concentration faster (after 30–60 min), and has a shorter duration of action (2–5 h) than regular human insulin (12, 25, 27). Its pharmacodynamic (PD) profile in children and adolescents is similar to that seen in adults (12, 26, 28–30). The adult pharmacokinetic (PK) data and the pediatric PD data for insulin lispro are consistent with those of insulin aspart and insulin glulisine in pediatric patients (31, 32). The pharmacological profiles of the three rapid-acting insulin analogs are not considered to translate into significant clinical differences, although the three agents have different chemical properties (2, 33). The recommended time of administration of insulin lispro is 0–15 min before a meal (12, 18), but it can alternatively be given immediately after meals if needed (12, 18).

To achieve optimal prandial but also basal glycemic control, due to its short duration of action, bolus injections of insulin lispro need to be integrated into an insulin regimen that includes long-acting insulin, injected once daily (QD) or BID. It can also be delivered by CSII (18), which allows insulin lispro to cover both basal and bolus insulin needs.

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Two single-dose trials provided evidence that postprandial injection of insulin lispro achieves lower 2 h postprandial BG excursions than regular human insulin injection before the meal. Insulin lispro, when given before or after the meal, resulted in similar postprandial BG excursions (26, 30). In another RCT (Table S1) (13), 60 prepubertal children received a basal-bolus insulin regimen, using an average of two daily injections of either pre or postprandial insulin lispro, or preprandial regular human insulin during three crossover periods. Preprandial insulin lispro was more effective in lowering the 2 h postbreakfast BG levels, followed by postprandial insulin lispro and preprandial regular human insulin (p < 0.001, respectively; Table S1).

HbA1c control. One systematic meta-analysis by Singh et al. (58), analyzing five individual crossover RCTs (13, 14, 41–43) with data from more than 600 pediatric patients treated with insulin lispro, and four additional small RCTs (40, 44–46), showed that insulin lispro achieved similar HbA1c levels as regular human insulin across all age-groups (Table S1). Due to the short treatment periods (usually 3–4 months), and the fact that NPH was used as the basal insulin at various frequencies (1–3 times/day), only minor changes in HbA1c were observed in these trials (Table S1). Only 1 RCT published in 2011 and including children aged 4–17 years has compared insulin lispro with another short-acting analog. In this study, insulin glulisine, given as part of an MDI regimen with insulin glargine or NPH insulin BID as the basal component, was non-inferior to premeal insulin lispro for HbA1c control (33).

Longer-term and real-life data on the use of insulin lispro over 1–3 years in various basal-bolus regimens with either NPH insulin or insulin glargine are available from six non-RCTs (prospective and retrospective observational studies), in age groups between 0 and
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Fig. 2. Seven-point blood glucose profiles obtained during a threefold crossover RCT in 60 prepubertal children (2–11 years) who received basal insulin [neutral protamine Hagedorn (NPH), lente or ultralente, average two injections per day] plus mealtime injections (average two injections per day) of either insulin lispro within 15 min before the meal, insulin lispro immediately after the meal, or regular human insulin 30–45 min before the meal [data from Deeb et al. 2001 (13)]. \( \ast p < 0.001 \) for insulin lispro before meals vs. regular human insulin; \( \ast \ast p = 0.023 \) for insulin lispro before meals vs. insulin lispro after meals; \( \ast \ast \ast p = 0.037 \) for insulin lispro after meals vs. regular human insulin; \( \ast \ast \ast \ast p = 0.006 \) for insulin lispro before meals vs. regular human insulin.

18 years (50–55). Evidence of improved glycemic control after switching to insulin lispro from regular human insulin in MDI or CSII regimens comes from a large retrospective observational study that included 884 children, adolescents, and young adults (largest group: 414 children aged 5-12 years) who were observed for up to 6 years (50). A significant decrease in HbA1c of up to \(-0.7\%\) was observed over a period of 2 years after the switch to insulin lispro in the 5–12 years age group, whereas a decrease of \(-0.2\%\) was observed in patients of the same age group treated with regular human insulin.

Hypoglycemia during MDI treatment. As for any insulin, hypoglycemia is the most frequent undesirable effect associated with insulin lispro (12). In the systematic meta-analysis by Singh et al. (58) mentioned above, and in five additional pediatric RCTs evaluating insulin lispro vs. regular human insulin (13, 40, 44–46), overall hypoglycemia and nocturnal hypoglycemia rates were similar or less frequent with insulin lispro than with regular human insulin (Table S1). Two RCTs showed a significant reduction in nocturnal hypoglycemia with insulin lispro vs. regular human insulin, in children (incidence 8% vs. 13%) (41) and in adolescents (rate 1.0 vs. 1.7 episodes/30 days) (33). The overall hypoglycemia rate was reduced with insulin lispro vs. regular human insulin in a meta-analysis of adult and adolescent data (59), and in one additional RCT in adolescents not included in that meta-analysis (40). Severe hypoglycemic episodes were generally rare and incidences, when reported, did not differ between insulin lispro and regular human insulin. In the other RCTs there were no significant differences between insulin lispro and regular human insulin, or between insulin lispro and insulin glulisine for nocturnal, overall, or severe hypoglycemia (Table S1). An early publication, in 1998, reported two cases of adolescents presenting with severe hypoglycemia immediately after the prebreakfast injection of insulin lispro (60), but in several non-RCTs or retrospective studies in children, adolescents, and young adults, severe hypoglycemia was rare and its incidence did not increase when patients were switched from previous treatment to insulin lispro (50–54, 61).

Diabetic ketoacidosis during MDI treatment. No cases of diabetic ketoacidosis (DKA) were reported in any of the 10 pediatric RCTs evaluating the use of insulin lispro as part of an MDI basal-bolus regimen (Table S1), and only four cases were reported in three out of eight other prospective trials (48, 52, 55). These data indicate that the risk of DKA is low in MDI regimens with insulin lispro if insulin doses and BG values are monitored appropriately.

Treatment preference. Three of the 10 pediatric RCTs evaluating insulin lispro as MDI treatment (Figure 1) provided data on which treatment was preferred by patients or their families. In two of these studies, patients or their families preferred insulin lispro over regular human insulin (42, 43). In the third study, patients preferred an additional premeal injection of insulin lispro before the afternoon meal over no additional injection (46). Summary. A total of 20 prospective trials, including 10 RCTs, have shown that MDI treatment with insulin lispro, mainly using NPH insulin as the basal component, was associated with significantly decreased postprandial glucose excursions, similar or improved HbA1c levels, and similar or reduced risks of hypoglycemia when compared with regular human insulin across all pediatric age-groups.

Efficacy and safety of insulin lispro in pediatric populations treated with CSII regimens

The use of insulin pumps in children and adolescents is increasing, especially for infants and toddlers. Through 24 h-adjustable basal insulin rates and additional patient- or parent-activated bolus doses at mealtimes, CSII treatment is considered to enable a more physiological insulin release than MDI regimens (15, 62). Common reasons for switching from MDI to CSII
| Insulin lispro for CSII treatment | 21 prospective trials |
|----------------------------------|----------------------|

**7 RCTs evaluating CSII treatment with insulin lispro vs. non-CSII MDI regimens:**
- 1 trial, N=36, age 9-18 years: CSII with insulin lispro or aspart, vs. MDI with mealtime regular human insulin and basal insulin glargine QD (bedtime) (64)
- 1 trial, N=23, age 9-14 years: CSII with insulin lispro, vs. MDI with mealtime regular and basal NPH insulin (65)
- 3 trials, N total=77, across all age groups: Starting CSII with insulin lispro vs. continuation on any MDI (66-68)
- 1 trial, N=10, age 7-10 years: CSII with insulin lispro from dinner throughout the night, combined with prebreakfast injection of NPH and lispro, vs. MDI with insulin and basal NPH BID (69)
- 1 trial, N=23, age 12-35 years: CSII with insulin lispro, vs. MDI with 3 mealtime rapid-acting insulin injections and NPH QD (bedtime) as basal insulin (70)

**2 RCTs evaluating CSII treatment with insulin lispro vs. other CSII regimens:**
- 1 trial, N=298, age 4-18 years: CSII with insulin lispro vs. CSII with insulin aspart (71)
- 1 trial, N=27, age 1.8-9 years: CSII with insulin lispro vs. regular human insulin (72)

**9 non-RCTs and observational studies evaluating the switch from MDI to CSII treatment:**
- 4 studies, N total=363, across all age groups: Switched from various MDI regimen to CSII with insulin lispro (73-76)
- 1 study, N=42, age 4.5-17 years: Switched from MDI to CSII with insulin lispro or aspart, up to 4 years of follow-up (77)
- 2 studies, N total=55, toddlers (N=46 <6 years, N=9 <40 months): Switched from MDI to CSII with insulin lispro (78,79)
- 1 case-control study, N=80, adolescents: Initiation of CSII with insulin lispro vs. initiation of MDI (80)
- 1 study, N=17, adolescents: Switched from MDI to CSII with insulin lispro or aspart, up to 4 years of follow-up (81)

**2 non-RCTs evaluating the start of CSII treatment with insulin lispro after diagnosis of T1DM:**
- 1 study, N=28, age 2-32 years (N=2 >18 years): Initiation of CSII with insulin lispro as early as 1 day after diagnosis of T1DM (82)
- 1 case-control study, N=12, toddlers (6-30 months): Initiation of CSII with insulin lispro vs. initiation of MDI (83)

**1 non-RCT evaluating the dosage of basal and bolus insulin during CSII treatment:**
- Non-RCT, N=100, age 1.6-18 years: CSII treatment with insulin lispro or aspart (84)

Fig. 3. Prospective trials with insulin lispro in CSII treatment of children and adolescents with type 1 diabetes. Abbreviations: BID, twice daily; CSII, continuous subcutaneous insulin infusion; N, number of patients in study; NPH, neutral protamine Hagedorn; QD, once daily; RCT, randomized controlled trial. *Supplemental Table S2 provides details regarding design and results of these studies.

Treatment include recurrent hypoglycemia, a desire for a more flexible lifestyle, and the need for improved glycemic control (63).

To date, insulin lispro has been used for CSII treatment of children and adolescents with type 1 diabetes in 21 prospective clinical trials (64–84) (Figure 3). These include seven RCTs specifically comparing CSII treatment with insulin lispro vs. non-CSII MDI regimens (64–70) and two RCTs comparing CSII treatment with insulin lispro vs. other CSII regimens (71, 72) with a total of 494 patients across all age-groups, including young adults (Table S2).

For children treated with an MDI regimen and switched to CSII, basal insulin rate requirements are usually less than 50% of total daily insulin dose requirements, which vary according to age, C-peptide levels, baseline HbA1c, and diabetes duration (85, 86). Younger children (aged 3–9 years) may need higher basal rates in the evening and early in the night, while adolescents may need an increase in the early morning, attributed to the classical dawn phenomenon (86).

**Glycemic control with CSII treatment.** As reviewed by Kaiserman et al., in 26 studies with more than 2500 pediatric and adolescent patients, CSII treatment with insulin lispro consistently showed improved or similar glycemic control vs. any type of MDI regimen, similar glycemic control vs. CSII with insulin aspart (62), decreased postprandial BG excursions, and achieved better parent satisfaction vs. CSII with regular human insulin (72). These included seven RCTs evaluating the use of insulin lispro during CSII treatment vs. non-CSII MDI treatment in the various age-groups (Table S2; all included in the Kaiserman review) (64–70).

**Blood glucose control.** During CSII treatment with insulin lispro, postprandial BG control overall was not different from BG control during MDI treatment. However, in two studies, CSII treatment with insulin lispro achieved significantly better control of BG levels after breakfast and at 03:00 hours than MDI treatment with insulin lispro and NPH insulin (69), and significantly better control of BG after dinner than CSII treatment using regular human insulin (72). In a study conducted in patients already on CSII treatment, insulin aspart was non-inferior to insulin lispro regarding HbA1c levels, and showed similar self-measured BG profiles (71) (Table S2).
**HbA1c control.** HbA1c improvement, mostly vs. previous MDI treatment, was seen with insulin lispro for CSII in 12 additional prospective non-RCTs in toddlers, children, and adolescents across all age groups, including long-term studies with treatment for up to 10 years (73–84), and also in 7 retrospective studies analyzing routine pediatric care data (63, 86–91). The survey by Danne et al. showed that glycemic control during CSII treatment (45% of patients receiving insulin lispro) was better in preschoolers (n = 142) and in pre-adolescents (n = 321) than in adolescent patients (n = 578) (63). Also, a 3-year retrospective observational study showed a significant reduction in hospital admissions with CSII when compared with MDI treatment (87).

**Use of CSII treatment in toddlers.** Because of its flexibility, CSII treatment has become the preferred option for treating infants and toddlers. In a cohort of 66 children younger than 6 years at diagnosis, CSII treatment allowed better long-term metabolic control and lower risk of severe hypoglycemia than MDI, especially when CSII was initiated at diagnosis (91). One RCT specifically evaluated insulin lispro in 42 toddlers treated with CSII (aged 1.8–4.7 years) vs. MDI treatment (any regimen) as comparator. Mean HbA1c levels decreased in both treatment groups. After 3 months, patients in the CSII group had significantly lower HbA1c than patients in the MDI group (HbA1c 8.4% vs. 8.8%), but after 6 months the difference was no longer significant (67). In addition, insulin lispro was used for CSII treatment of toddlers in 3 non-RCTs, in a total of 67 patients (78, 79, 83). Two studies described decreases in HbA1c (78, 79) and less severe hypoglycemia (70) compared with prestudy treatment with a non-pump regimen. One case–control study in toddlers initiating insulin treatment described similar glycemic control with CSII and a conventional insulin regimen (83). Current guidelines indicate that CSII treatment for type 1 diabetes can be successfully used even in young infants when adequate education and support are provided for the caregivers (1, 2, 73). A few recent case reports have described the effective and safe use of insulin lispro diluted to 10 IU/mL for CSII treatment in neonates (two cases) (92) and in a 2.5-year-old boy requiring a very low insulin dose (93).

**Hypoglycemia during CSII treatment.** Data from seven RCTs (64–70), seven prospective non-RCTs (73–79), and six retrospective studies in real-life conditions (63, 86–88, 90, 94) showed that, when switching children from an MDI regimen to CSII treatment with insulin lispro, overall hypoglycemia and nocturnal hypoglycemia rates were similar or less frequent with insulin lispro (Table S2).

In RCTs, severe hypoglycemia rates of 0.1–0.3 episodes per patient-year were reported during CSII treatment with insulin lispro, similar to those in the comparator arms (0.1–0.5 episodes per patient-year) [Table S2; (62)]. Six prospective non-RCTs documented a significant reduction of severe hypoglycemic events (73, 75, 76, 78–80) after switching to CSII treatment. One study showed a numerical reduction of any hypoglycemic episodes (74), and two other studies found no change in rates of severe (77) or any hypoglycemia (81) after switching to CSII treatment. In real-life, the largest cross-sectional retrospective study, by Danne et al. from 2008, measured an incidence of 6.6 events of severe hypoglycemia per 100 patient-years during CSII treatment in 1086 patients treated either with insulin lispro, aspart, or regular human insulin (63). The incidence varied between different age-groups and was highest in preschool children (10.8/100 patient-years) (63). However, the overall incidence was much lower than in the older Hvidore study from 1997 (22/100 patient-years) (95).

In toddlers specifically, one RCT found that the incidence of BG values <60 mg/dL did not significantly differ between CSII treatment (after switching from MDI treatment) and MDI treatment arms (bolus insulin lispro used in both cases) (67). Events with BG measurements <100 mg/dL but no documented hypoglycemic symptoms were more common in the CSII arm; however, the authors questioned the clinical significance of this finding (67). Two non-RCTs, including a total of 55 toddlers, documented a significant reduction in severe hypoglycemia, despite tighter HbA1c control after switching to CSII treatment (78, 79), and one case–control study in 12 toddlers found at least a trend toward fewer episodes of severe hypoglycemia (83).

**Diabetic ketoacidosis during CSII treatment.** Few DKA events were reported during RCTs of CSII treatment with insulin lispro (Table S2). In the largest RCT, by Weinzimer et al., 2 of 100 patients on insulin lispro (2%) and 1 of 198 patients on insulin aspart (0.5%) experienced one DKA episode each during the 16-week CSII treatment period (71). In the eight smaller RCTs of CSII treatment with insulin lispro, only a single episode of DKA was reported (68). In the 12 non-RCTs and observational studies (designs shown in Figure 3), the reported DKA episodes during CSII treatment with insulin lispro varied from none in five studies (78, 81–84) to 5 of 51 patients in a German patient education study (73). In eight retrospective studies, the incidence varied from none in four trials (87, 88, 90, 96) to 6.3 events of DKA per 100 patient-years in the largest retrospective study, by Danne et al. mentioned above (63). Recent studies have shown that the risk of catheter obstruction was not increased with insulin lispro compared with other rapid-acting insulin analogs (97).
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Treatment preference. Of the two RCTs evaluating insulin lispro for CSII treatment vs. other CSII regimens (Fig. 3), data on treatment preference are only available from one study in very young children (72). In this study, 74% of affected parents preferred to continue CSII treatment with insulin lispro rather than with regular human insulin.

Summary. CSII treatment with insulin lispro showed similar or improved glycemic control when compared with MDI or other CSII regimens across all age-groups, without increasing the rate of severe hypoglycemia.

Specific safety aspects

Allergies and skin reactions. Allergic reactions can occur in pediatric patients with type 1 diabetes with any type of insulin, and the immunogenicity of insulin lispro is similar to that of other insulins (regular human insulin, NPH insulin, insulin aspart) in terms of antibody formation (98). Interestingly, in three case reports, allergic reactions that developed during regular human or NPH insulin treatment ameliorated after switching either to insulin lispro injections (99) or to insulin lispro CSII treatment (100, 101).

Lipodystrophy (atrophy or hypertrophy) at the injection site, another complication associated with subcutaneous injections or infusions of insulin, is uncommon during treatment with insulin lispro (1/1000 to <1/100 patients) (12). If insulin is injected into areas of lipohypertrophy, insulin absorption is likely to be modified and can lead to erratic glycemic control. In a long-term, open-label, non-RCT where 42 patients were followed during 4 years of CSII treatment with insulin lispro, 60% of patients developed minor signs of lipohypertrophy and 23% developed local skin reactions, but no systemic reactions were reported (77). However, a retrospective study reported fewer lipohypertrophy reactions during the first year of CSII treatment with insulin lispro than during the pre-CSII period with prandial injections of insulin lispro (4.2 vs. 27.2 events per 100 patient-years, p < 0.003) (88).

Lipoatrophy has been reported rarely during insulin lispro CSII treatment (100, 101). In this study, 74% of affected parents preferred to continue CSII treatment with insulin lispro rather than with regular human insulin. In adults, insulin analogs are mainly compared with regular human insulin. In children, due to the different PKs of the two insulins and testing at different injection times, including injection before a meal. In addition, the systematic meta-analysis by Singh et al., evaluating RCTs with insulin lispro as MDI treatment (58), included different studies when evaluating HbA1c control and hypoglycemia, making it difficult to compare outcomes between insulin lispro and regular human insulin. However, for each set of studies, the meta-analysis described the relative outcome for each parameter for insulin lispro vs. regular human insulin. In adults, insulin analogs are short-term data, but longer-term efficacy and safety data are available from large ‘real-world’ studies. Over time, pediatric diabetologists have optimized components of insulin treatment regimens to further improve glycemic control and reduce glycemic variability through better control of postprandial BG excursions. Regimens have been intensified with increased use of MDI and CSII (112, 113), taking advantage of rapid-acting insulins’ PD profiles. For example, in 2012, 75% of all pediatric patients in the German/Austrian Prospective Diabetes Follow-Up Registry had used rapid-acting insulins (114). As a result of these strategies, variable reductions in mean HbA1c values have been observed in various nationwide studies from France (no significant decrease over 10 years, range 8.2–8.5%) (112), Germany/Austria (mean decrease from 8.9% to 8.0% over 18 years (114), and from 8.7% to 8.1% over 15 years (115), and Slovenia (mean decrease ranging from 9.3% to 7.8% over 12 years) (116). In the United States, the mean HbA1c levels achieved in the most recent assessment varied considerably with age, ranging between 8.1% in 7-year-old children and 9.2% in 19-year-old adolescents (117).

Discussion

Since insulin lispro was introduced as the first rapid-acting insulin analog almost 20 years ago, its efficacy and safety have been established for adults and pediatric patients without any age limits (12). Overall, 41 prospective studies (RCTs and non-RCTs) are available evaluating the use of insulin lispro in children and adolescents (20 MDI, 21 CSII). In these studies, insulin lispro was mainly compared with regular human insulin in the standard regimens of the time, with basal insulin coverage usually provided by intermediate-acting NPH insulin. Most RCTs included only a small number of patients and were of short duration, which limited their power to demonstrate statistically significant differences, especially on hypoglycemia rates. Lack of treatment blinding was an additional limitation for most RCTs. However, blinded studies were not possible for rapid-acting analogs vs. regular human insulin, particularly in children, due to the different PKs of the two insulins and testing at different injection times, including injection before a meal. In addition, the systematic meta-analysis by Singh et al., evaluating RCTs with insulin lispro as MDI treatment (58), included different studies when evaluating HbA1c control and hypoglycemia, making it difficult to compare outcomes between insulin lispro and regular human insulin. However, for each set of studies, the meta-analysis described the relative outcome for each parameter for insulin lispro vs. regular human insulin. In adults, insulin analogs are

"Real-world" data on the long-term use of insulin lispro and rapid-acting insulins in general

The clinical trials evaluating the use of insulin lispro and other rapid-acting insulins mainly provided...
recommended for the treatment of type 1 diabetes to reduce the risk of hypoglycemia (118). Studies in children are of small size and short-term, and therefore it is more difficult to draw clear conclusions. Based on the available short-term RCT data alone, the benefit of rapid-acting insulin analogs over regular human insulin in terms of glycemic control could be considered as controversial. However, in general, rapid-acting analogs may reduce the risk of hypoglycemia when used in MDI treatment, and of severe hypoglycemia when used in CSII treatment, and they facilitate treatment. Switching from MDI to CSII treatment also allows better glycemic control. The widespread use of rapid-acting analogs in children in the real-world setting indicates that they do represent an improvement for the care of children and adolescents with diabetes (2). For example, based on the recent EXCHANGE study, less than 1% of children in the United States who require insulin MDI or CSII treatment for type 1 diabetes still use regular human insulin as short-acting insulin (117).

In pediatric clinical trials, insulin lispro allowed better control of postprandial glucose excursions vs. regular human insulin, and allowed less variation of glucose levels during the day, with HbA1c reductions close to those described in adult studies (15, 17). Compared to adults, children and adolescents with type 1 diabetes have unique requirements that vary according to age groups and require individualized care plans with ongoing education and support (1–3).

The increasing use of insulin lispro and other analogs to optimize MDI and CSII regimens, together with advances in BG monitoring, now allow patients, clinicians, and families to reach HbA1c targets more safely than during the early days of intensive insulin therapy (119). In addition to early RCTs, pediatric data with these optimized insulin regimens are becoming available from ‘real-world’ experience and long-term observational studies. These data provide evidence that glycemic control has improved and that the risk of hypoglycemia has decreased with regimens using insulin analogs (114–116). Families and physicians now have a larger choice of insulin regimens to better meet the individual child’s needs, and to improve overall glycemic control without increasing and even decreasing the risk of hypoglycemia. As a consequence, patients and parents consistently preferred insulin lispro over regular human insulin in MDI or CSII regimens in RCTs and non-RCTs (42, 43, 46).

Further broadening of treatment options can be expected, based on recent developments in the treatment of adult type 1 diabetes. These include advances in CSII treatment technology, combining continuous glucose monitoring and semi- or fully-closed loop systems (120–123), and also development of ultra-long and ultra-rapid insulin analogs (124), all of which could benefit the unpredictable lifestyle of a child. Several efforts to build an ultra-rapid insulin have been tested in adults (124), but no data have yet been published in children. However, because pediatric clinical research has now become a regulatory requirement – a Pediatric Investigation Plan has to be provided to the regulatory authorities for each new drug submitted that can potentially be used in the pediatric population – studies of these new insulins will add data to the body of pediatric diabetes literature available on use of insulin lispro and other rapid-acting insulins in MDI and CSII regimens.

Finally, currently recommended HbA1c targets for children differ between geographic regions (119, 125), and efforts to harmonize and improve pediatric diabetes care in the future are underway. In June 2014, the ADA lowered HbA1c targets for children with type 1 diabetes, according to current ISPAD HbA1c targets (126). An example from Europe is the SWEET program, which aims to establish European Reference Centers and networks for pediatric diabetes treatment. Once implemented, benchmarking of carefully defined quality-of-care indicators is expected to allow further refinement of current ISPAD guidelines and to help to optimize evidenced-based care for children with diabetes (125).

In conclusion, insulin lispro has contributed significantly to improvements in insulin regimens for pediatric patients with type 1 diabetes, with more physiological insulin administration, allowing these patients to safely reach better glycemic control, with more flexibility in their daily lives.

Acknowledgements

We thank Trilogy Writing and Consulting GmbH, Frankfurt, Germany, for literature search and medical writing support on behalf of Eli Lilly and Company. We thank Dominique Levesque, BioMedicines Medical Information, Lilly France, Neuilly-sur-Seine, France, for supporting the programming and conducting the literature search.

Conflicts of interest

Heike Jung, Imane Benabbad and Myriam Rosilio are Eli Lilly employees and also own Eli Lilly stock. Kevin Kaiserman conducts clinical research and is a speaker and consultant for Medtronic Diabetes. Michel Polak and Beate Karges have no conflicts of interest to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Detailed methodology.

Fig. S1. Overview of systematic literature search and study selection process.
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Table S1. Efficacy and safety of multiple daily injection (MDI) treatment with insulin lispro vs. comparator therapy in children, adolescents, and young adults with type 1 diabetes, in RCTs with treatment periods ≥4 weeks

Table S2. Efficacy and safety of CSII treatment with insulin lispro vs. comparator in children, adolescents, and young adults with type 1 diabetes, in RCTs with treatment periods ≥4 weeks

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