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# Treatment of type 1 diabetes in children and adolescents using modern insulin pumps

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ABSTRACT

In the last decades, we are experiencing an increasing use of insulin pumps for the treatment of type 1 diabetes in children and adolescents. The most frequent reasons for switching from insulin injection schemes to pump therapy are frequent and/or severe hypoglycaemia, dawn phenomenon, poor glycaemic control, wish for more flexibility in daily life, and needle phobia. In toddlers and preschoolers, pumps are frequently introduced from the onset of type 1 diabetes. Pumps offer the possibility of adjusting basal insulin rates individually on an age-depended manner as well as of optimizing meal-related insulin requirements according to the meal composition by using three different kinds of boluses. Structured and intensive education of patients and their families on basics and specific requirements of insulin pump therapy is essential in order to get them familiar with the devices and their features. There is increasing evidence both from multicentre cross-sectional studies as well as from meta-analyses of randomized clinical trials in paediatric populations showing that patients with pump therapy can achieve a more favourable metabolic control accompanied with less hypoglycaemic events than those with multiple daily injections.



## 1. Introduction

The achievement of long-term near-glycaemic control in patients with type 1 diabetes (T1D) is of great importance to reduce the risk of diabetes-related micro- and macrovascular complications [1–3]. In current clinical practice, the use of intensified insulin treatment in terms of multiple daily injections (MDI) is the standard treatment not only in adult, but also in young patients with type 1 diabetes from onset of the disease [4]

In the last decade, we are experiencing an increasing use of insulin pumps (continuous subcutaneous insulin infusion, CSII) for the treatment of type 1 diabetes in children and adolescents. In Germany, the number of paediatric patients carrying a pump has been doubled every year since 2000 [5]. Theoretically, CSII offers the most physiologic way of insulin delivery due to its ability to more closely simulate the normal pattern of insulin secretion, namely, continuous 24-hour adjustable "basal" delivery of insulin superimposed with prandial-related "boluses". In addition, CSII offers more flexibility and more precise insulin delivery than MDI. First experiences with CSII treatment in young patients with diabetes were gathered in the United States with adolescents who participated at the Diabetes Control and Complication Trial (DCCT). Boland et al. reported not only a significant improvement of glycaemic control within one year, but also a pronounced reduction of the incidence of severe hypoglycaemia in adolescent patients with insulin pump treatment compared to those with MDI [6].

Nowadays the most frequent reasons for switching from insulin injection schemes to CSII are frequent and/or severe hypoglycaemia, dawn phenomenon, poor glycaemic control, wish for more flexibility in daily life, and needle phobia [7,8]. While in the beginning of the insulin pump era most pae-

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diatric diabetologists started CSII in adolescents, today there are mainly young children set on this kind of treatment. In toddlers and preschoolers, CSII is frequently introduced from the onset of type 1 diabetes, as it provides not only high treatment flexibility combined with less painful procedures, but also the possibility of delivering precisely very small amounts of insulin compared to treatment using insulin injections [9]. In our centre, about sixty percent of paediatric patients with type 1 diabetes are treated with CSII, and even seventy percent of children below 6 years are using insulin pumps.

## 2. Clinical practice of CSII

The setup of insulin treatment using insulin pump differs substantially from centre to centre and it is based more on empirical experience of the paediatric endocrinologists rather than on standardized evidence-based data. [10–12]. In several studies it has been shown that hourly insulin basal rates depend on the age of the patients and differ from those in adult patients [13–15]. Adolescents have got high basal rate needs in the first morning hours (dawn phenomenon) as well as in the evening (dusk phenomenon), while toddlers need high basal rates in the second half of the day. However, there is no general consensus on how much insulin should be delivered as basal rate in childhood and adolescent pump therapy. The basal rate covers the food-independent insulin requirement, which is predominantly dependent on hepatic gluconeogenesis. In a practical way, the correct dosing of the basal rate can be identified if every food intake (even a small snack) necessitates an extra food bolus and, on the other side, skipping a meal should not lead to hypoglycaemia. In order to check the correct dosing of a programmed basal rate, fasting tests can be performed. Test procedures are described in Table 1. According to the treatment concept of our centre, basal rate should not exceed 30% to 40% of the total daily insulin dose, while the prandial insulin need is usually more than 50% to 60% of the total dose. Modern insulin pump devices offer the possibility of temporary adjustment of the basal rate, e.g. increase or decrease of the programmed basal rate over few hours, which is often necessary during periods of increased (acute infectious disease) or decreased (e.g. sport) insulin requirements, respectively.

In the insulin pump treatment, prandial insulin requirements are covered by applying a bolus. The prandial boluses are mainly dependent on carbohydrate intake (meal composition), circadian variation of insulin sensitivity, current blood glucose levels, and planned activity. Usually, the amount of insulin per gram carbohydrate is highest in the morning, lower for lunch and higher in the evening. Accordingly, patients with CSII need a dosing scheme that helps them to calculate the appropriate dose. In most of the current pump devices, a bolus calculator functionality is established in order to allow the physician and the user to programme individual insulin sensitivity data and carbohydrate ratios as well as target glucose levels that can be used by the patient to get an adequate insulin dosing. Moreover, the calculator uses a scientific 'adjustable insulin action curve' to keep track of previously delivered insulin that is still 'active' in the body, and considers this information before providing a dosing recommendation to patients. The calculator manages the necessary calculations for patients using a blood glucose reading, carbohydrate entry, or both. By this functionality, the use of insulin pumps is simplified, particularly for young patients, even when complex insulin calculation procedures are required.

**Table 1 – Fasting test procedures to check correctness of programmed basal rate in CSII.**

| | |
|---|---|
| Duration of test | 6 hours |
| Start of test | 2 (3) hours after last meal |
| Composition of last meal prior to test | mainly carbohydrates, not exceeding 40 g |
| Blood glucose at start of test | lower than 180 mg/dl [10 mmol/l] |
| Blood glucose measurement during test | every hour |
| Conditions during test | no physical exercise, fluids and small amounts of legumes are allowed |
| Interruption of test | in case of symptomatic hypoglycaemia, blood glucose below 50 mg/dl [2.7 mmol/l] or hyperglycaemia with ketonuria/ketonemia |

Moreover, modern insulin pumps offer the ability of the application of a meal-related insulin bolus in three different ways. In standard or normal bolus, insulin is delivered rapidly as a shot and in square-wave bolus over an extended period of time. A dual-wave or combination bolus combines a single shot as well as insulin delivery over an extended period of time. Thus, the kind of bolus can be chosen according to the meal composition for an optimal adjustment of the meal-related insulin needs. O'Connell et al. found better post-prandial glycaemic profiles and a lower risk of hypoglycaemia when using square-wave bolus (50% as single bolus and 50% prolonged over 2 hours) for meals with low glycaemic index (GI) compared with standard bolus [16]. For high-caloric fat-rich meals, the use of a dual-wave bolus has been found as the most effective method of insulin administration [17]. In this study, Chase et al. analyzed the 6-hour postprandial glucose profiles in nine patients after a standardized meal high in carbohydrates, calories and fat using four different ways of insulin administration: (a) standard bolus 10 min prior to the meal, (b) two separate boluses of one-half the same total dose (the second after 90 minutes), (c) entire bolus given as square-wave over 2 hours, and (d) dual-wave (70% as a bolus and 30% as square-wave over 2 hours). In a recent publication, Pańkowska et al. reported lower haemoglobin A1c levels in patients using dual-wave or square-wave boluses at least once per day than in patients using normal bolus [18].

## 3. Choice of insulin and catheters in CSII

The majority of paediatric patients with CSII use short-acting insulin analogs [7,19]. In the PedPump Study, 91 percent of

pump users had a short-acting insulin analog. In Germany, all three analogs insulin lispro, insulin aspart, and insulin glulisine are approved for CSII. Reasons for preferring short-acting analogs are rapid fluctuations of blood glucose levels which are common in paediatric diabetes. This necessitates the opportunity of rapid adjustment of the insulin dose to the current metabolic situation. Moreover, in daily clinical practice, parents report high flexibility in insulin treatment management, which is frequently required for spontaneous and unpredictable eating behaviour of young children. Due to the short acting profiles of these insulin analogs, risk of hypoglycaemia does not increase despite of frequent boluses. Rapid-acting analogs are available only in the U100 concentration (100 units per ml). If the basal rate per hour is rather low, such as 0.05 or 0.1 units per hour, this low fluid throughput may lead to a faster catheter obstruction compared with more dilute insulin and a higher fluid throughput. An alarm of catheter obstruction usually appears only after 2–4 units, in some cases 8 units. Particularly, in neonates or toddlers or during low insulin requirements like during the period of the partial remission phase, such an occlusion may therefore take several hours at a low hourly basal rate. To avoid this problem, an insulin dilution may be prepared using an insulin-free medium. The stability of a mixture of insulin aspart (U100) with a diluent prepared for diluting neutral protamine Hagedorn (NPH)-insulin resulting in a U10 and U50 concentration was studied in a simulated continuous insulin infusion for 7 days at 37°C with MiniMed® 508 insulin pumps. Both insulin mixtures sustained their biological potency of above 97% after 7 days. No significant degradation of insulin aspart or catheter obstructions was observed [20]. Although similar studies with insulin lispro mixtures with the respective sterile diluent (Sterile Diluent ND-800) are not published yet, it has been used for this purpose in single cases successfully [21]. These diluents can be obtained through direct contacts with respective pharmaceutical companies.

Disconnectable catheters are preferred by children and adolescents due to their frequent physical exercise and outdoor activities. The length of the needle is of great practical importance. Children have significantly less subcutaneous fat than adults. Therefore, the preferred needle length is 6–8 mm. If frequent catheter problems occur or if the overall success of CSII is below expectations, one should always try longer needles, especially in adolescents. Teflon catheters are preferred by many children that are afraid of wearing a steel needle in their body. However, it appears that catheter obstruction may be less with steel needles, in toddlers and preschoolers, although controlled studies are lacking. It is recommended to change catheters every two to three days.

## 4. Electronic readout of pump memory to adjust insulin therapy

The opportunity to have electronic memory readout of all entries and alarms for up to 90 days is a special feature of the newer pump models. When used in analyses for study purposes [7,14], such readouts have demonstrated a close correlation between the number of daily boluses and HbA1c. This opportunity essentially leads to a "patient of glass" where every single manipulation of insulin therapy (or lack thereof) can be pinpointed with an exact record of time and dosage. It leaves the patient and the family without the opportunity to share only that information they wish to divulge, as is the case with conventional logbooks. To use this opportunity in a constructive fashion, a consent regarding this new way of monitoring insulin treatment needs to be found between the diabetes team, patient and his/her family. In the long run, the addition of electronic blood glucose data to this electronic record of insulin therapy will offer new ways of patient supervision and therapeutic management. The lack of privacy of glycaemic management of insulin therapy will offer new chances (e.g. telemedicine) but also raises concerns regarding data safety. Only a trustful collaboration between the diabetes team and the patients will result in a beneficial application of these technical opportunities. When applied correctly, these advances in information technology will change our current practice of insulin pump therapy in the near future.

## 5. Glycaemic control in young patients with CSII

Recent multicentre cross-sectional studies in thousands of young patients with CSII reveal lower average glycated haemoglobin levels than those reported in comparable studies in patients with multiple daily injections [7,22]. In the PedPump Study the average HbA1c of 1,041 patients with CSII was 8.0 ± 1.3% with better values in preschool (7.5 ± 0.9%) and pre-adolescent (7.7 ± 1.0%) children than in adolescent patients (8.3 ± 1.4%). In comparison, average glycaemic control levels in children and adolescents with multiple daily injections participated in the Hvidøre Study Group studies were 8.6 ± 1.6% and 8.7 ± 1.7% in 1995 (2,780 patients) and 1998 (2,101 patients), respectively. Although such a comparison should be regarded cautiously as one can assume that patients with CSII may have been biased by being motivated to carry an insulin pump, the results clearly show that the use of CSII can improve metabolic results in paediatric populations without increasing the risk of hypoglycaemia. Indeed, the rate of severe hypoglycaemia was up to 10fold lower in the PedPump Group than in the Hvidøre Group cohort [7,22].

In a multicentre, matched-pair cohort analysis comparing glycaemic control and adverse events of CSII with MDI in paediatric patients (434 pairs), Jakisch et al. demonstrated that CSII is a safe form of intensive insulin therapy with similar glycaemic effects, but with significantly reduced rates of hypoglycaemia and diabetic ketoacidosis (DKA) and lower insulin requirement when compared with MDI over a 3-year study period [23]. A phenomenon shown in this study as well as in other paediatric cohorts was a rapid decrease of HbA1c during the first months up to one year after the switch from MDI to CSII followed by a rebound of HbA1c at further follow-up [23,24]. Reasons for deterioration of initial therapeutic success could be missing of boluses, decreasing compliance with diabetes management requirements such as self-monitoring of blood glucose or erroneous eating be-

haviours. In the PedPump Study, HbA1c levels were inversely correlated with the number of daily boluses [7].

On the other hand there is evidence that particular groups of patients could sustainably profit from switching of therapy from MDI to CSII. Favourable metabolic results achieved with CSII can sustain for at least one year in young children aged below 12 years [24]. In our experience, parental supervision and support of diabetes management can help to achieve and maintain good glycaemic results in young children with CSII. In a retrospective paired study by Nimri et al., patients with elevated HbA1c levels (≥10.0%) at initiation of CSII experienced a significant decrease of HbA1c (–1.7%) with CSII, whereas those with low HbA1c (≤7.0%) did not [25]. Their findings indicate that in patients with good metabolic results under MDI, change to CSII could aim reduction of hypoglycaemia and increase of flexibility in daily life, whereas in those with poor glycaemic control under MDI introduction of CSII may lead to improvement of glycaemia. Analysis of the one-year data of 329 patients with MDI (at least 4 daily injections, 39.7% of the total cohort) and 329 patients with CSII (58.9%) in our centre revealed comparable average HbA1c levels between the two groups (Fig. 1). It may be assumed that patients accepting and taking advantage of CSII do represent a cluster with specific clinical and behavioural characteristics that make them different from MDI-treated patients in many respects. To our opinion, a diabetes care team experienced in both kinds of treatment can help patients finding the optimal form of intensified insulin therapy in order to achieve the best possible metabolic results accompanied by good quality of life.

Beyond of clinical experience, cross-sectional or longitudinal descriptive and comparative studies, there is an increasing amount of recent meta-analyses of RCTs including data of paediatric patients with CSII [26–29]. Previous meta-analyses were biased from lack of studies in paediatric patients [30,31]. In general, CSII is compared with MDI in terms of efficacy in glycaemic control and rate of severe hypoglycaemia. One has to take into account that the schemes of MDI regimens have been changed dramatically over the last two decades, particularly due to the introduction of short- and long-acting insulin analogs. In recent meta-analyses, RCTs with MDI treatment using short- and long-acting insulin analogs are included [26,28,29]. In the only meta-analysis including exclusively paediatric RCTs, Pankowska et al. found after short-term follow-up, that CSII is more effective than MDI regarding metabolic control (pooled weighted mean HbA1c reduction from MDI to CSII –0.24%, 95% confidence interval –0.41 to –0.07%) and allows reducing of the daily insulin requirements [28]. In a very recent evaluation from the Cochrane Metabolic and Endocrine Disorders Group including twenty three randomized studies (976 patients), a statistically significant difference was found in HbA1c favouring CSII (weighted mean difference –0.3%, 95% confidence interval –0.4 to –0.1%) without obvious differences between the interventions for non-severe hypoglycaemia. However, severe hypoglycaemia was reduced in those using CSII [29]. Pickup and Sutten clearly demonstrated that severe hypoglycaemia was reduced during CSII compared with MDI with a rate ratio of 2.89 (95% confidence interval 1.45 to 5.76) for RCTs and 4.34 (2.87 to 6.56) for before/after studies [26]. Interestingly, the highest reduction was found in those patients with history of severe hypoglycaemia on MDI and those with the longest duration of diabetes. Moreover, they found that the best improvement in HbA1c was in those patients with the highest HbA1c on MDI.

## 6. Quality of life and CSII

Introduction of insulin pump therapy in paediatric patients is mostly associated with high levels of satisfaction both in children and in their families. Patients and families report improvement of their quality of life (QoL). The possibility of sleeping as long as needed without interruptions for insulin

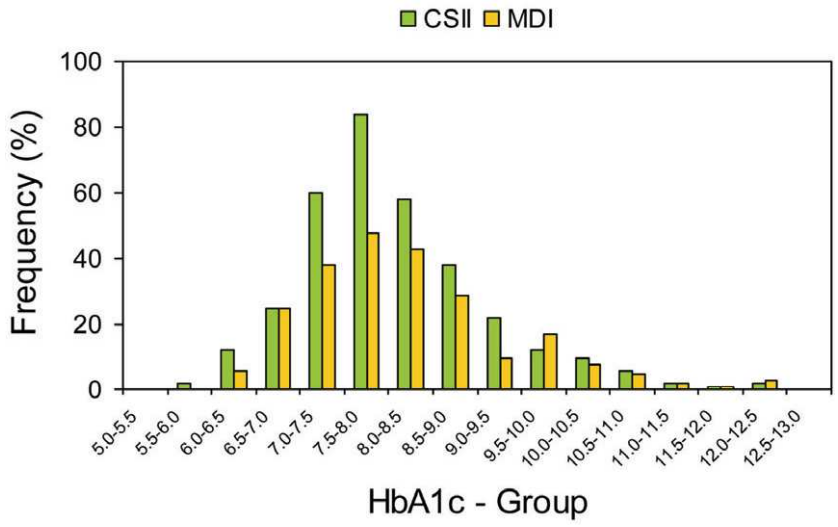


**Fig. 1 – Distribution of patients with multiple daily injections (MDI, *n* = 222) and continuous subcutaneous insulin infusion (CSII, *n* = 329) according to their mean HbA1c (data from the Diabetes Centre for Children and Adolescents of Hannover, Germany).**

injections, increased flexibility in meal timing, better adjustment of prandial insulin requirements according to the meal composition as well as frequent and painless correction of elevated blood glucose levels are some of the positive aspects of CSII for patients and parents. In a prospective study over two years, Linkeschova et al. evaluated quality of life using a validated diabetes-specific questionnaire (DSQOLS) and found that QoL was significantly improved with CSII when compared with MDI [32]. In a recently published study in 32 children starting on CSII at two Australian centres, Knight et al. reported on significant improvements not only in measures of metabolic control, mood and behaviour, but also in some complex cognitive skills after commencing CSII [33].

## 7. Outlook and conclusion

Since few years there is the possibility of combining insulin pump therapy with systems of continuous glucose monitoring (CGM), even in one device (sensor-augmented CSII, Paradigm® REAL-Time Insulin Pump and Continuous Glucose Monitoring System, Medtronic MiniMed Inc, Northridge, CA). CGM allows measurements of subcutaneous glucose concentration every one to five minutes and provides information about the magnitude, direction, duration, and frequency of glucose excursions as well as alarms for values exceeding preset levels. Theoretically, the combination of CGM and insulin pump treatment allows fine tuning of insulin delivery keeping high levels of flexibility without increase of painful procedures such as multiple finger-sticks or injections. So far, advantages of sensor-augmented pump therapy have been shown in a few studies [34], but not (yet) in a randomized clinical trial [35]. However, in that trial, successful sensor-augmented pump treatment as indicated by HbA1c below 7.0% was associated with good CGM compliance. Similar results regarding efficacy of CGM in dependence of continuous sensor application were also found in the Juvenile Diabetes Research Foundation CGM Trial [36,37]. In a multicentre RCT comparing conventional CSII with sensor-augmented CSII from the onset of type 1 diabetes (Paediatric ONSET Study), lower glycaemic variability and higher amounts of residual β-cell function measured as fasting C-peptide was found after 12 months of disease in those patients with frequent sensor usage [38]. At present, more RCTs are needed in order to define the efficacy of sensor-augmented pump treatment as well as the optimal time of introduction of this system for patients with type 1 diabetes.

In conclusion, there is an increasing use of modern insulin pump devices for the treatment of type 1 diabetes in children and adolescents. In the last few years, pump technology has been developed increasingly up to integrated systems of insulin pump and continuous glucose monitoring sensors, which represent an important pre-step of closed loop system treatment.

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## Conflict of interest

The authors have no conflict of interest to declare.

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