Running title:

Insulin pump therapy in CFRD

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Rapid communication:

Why is insulin pump treatment rarely used in adolescents and young adults with cystic fibrosis-related diabetes?

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Abstract

Background: In type 1 diabetes (T1D), continuous subcutaneous insulin infusion (CSII) increased steadily within the last years. Compared to conventional insulin injection regimes, major advantages might be a nearly physiological insulin secretion, lower rates of hypoglycemia, higher flexibility in daily life and increased quality of life. Data on CSII in cystic fibrosis-related diabetes (CFRD) are scarce.

Objective: To analyze current use of insulin pumps in CFRD and compare demographics of pump-treated patients between CFRD and T1D.

Methods: Data from the prospective German/Austrian diabetes patient registry on insulin-treated patients with either CFRD (n=515) or T1D (n=43,165) aged >10 years at manifestation of diabetes were analyzed.

Results: 4.1% (n=21) of CFRD and 17.7% (n=7,647) of T1D patients received insulin pump treatment within the recent year of care (p<0.001). Pump-treated patients with CFRD had a significantly shorter duration of diabetes (median [Q_1;Q_3]: 5.8 [2.9; 9.5] vs. 7.8 [4.3; 20.4] years, p=0.026) and tended to be younger (22.0 [18.2; 30.1] vs. 24.9 [17.3; 45.9] years) than pump-treated T1D patients. Age at initiation of CSII seemed to be lower in CFRD (19.2 [16.5; 29.2] vs. 23.3 [14.8; 43.5] years). Insulin pump therapy was used slightly more often in male CFRD patients than females (4.7 vs. 3.6%), whereas in T1D the opposite was observed (14.9 vs. 21.2%, p<0.001). Discontinuation rate of CSII was higher in CFRD than T1D (30.0 vs. 12.7%, p=0.005).

Conclusions: Despite potential advantages, insulin pump therapy was rarely used among adolescent and young adult CFRD patients.

Keywords: insulin infusion system, cystic fibrosis, diabetes mellitus, adolescent, young adult

Abbreviations

BMI – body mass index; BMI-SDS – body mass index standard deviation score; CFRD – cystic fibrosis-related diabetes; CT – conventional insulin therapy; MDI – multiple daily insulin injections; CSII – continuous subcutaneous insulin infusion; HbA1c – Hemoglobin A1c; T1D – type 1 diabetes mellitus; yrs – years.

INTRODUCTION

Among children and adolescents with type 1 diabetes (T1D), the frequency of insulin pump treatment rose continuously in recent years (1). Previous studies established continuous subcutaneous insulin infusion (CSII) as a safe and effective alternative to conventional insulin injection regimes in pediatric T1D patients (2,3). Insulin requirement and rate of hypoglycemic events are lower and quality of life increases with CSII (2,4). The effect on metabolic control is controversial (2,3,5). Nevertheless, CSII is the insulin regimen closest to the physiological insulin secretion.

In cystic fibrosis-related diabetes (CFRD), insulin is the only recommended medical therapy (6). Usually, it is delivered by multiple daily injections (6) which are a further burden for the patients. Eating patterns are irregular in CFRD due to varying appetite and gastrointestinal problems. To achieve the recommended high energy intake (6), patients consume several high-carbohydrate-containing meals and large snacks throughout the day. Hence, frequent insulin injections are required that discourage patients and may reduce carbohydrate intake. With CSII, multiple insulin boluses are possible without separate injections. Data on CSII in CFRD are scarce and mostly limited to case reports (7-11). However, fewer injections, a higher flexibility in timing, frequency and amount of eating and a more precise adjustment of basal insulin dose according to daily activity, infection status and individual needs might be several advantages of insulin pumps especially in CFRD. In addition, the ability to give continuous basal insulin during nocturnal enteral tube feedings and the availability of different bolus shapes (e.g. dual bolus for fat/protein-rich meals) might be further benefits.

Therefore, this study aimed to analyze current frequency of insulin pumps in CFRD compared to T1D. Furthermore, demographics of pump-treated patients were compared between groups.

METHODS

Data source and subjects

Data were retrieved from the computer-based, standardized, multicenter diabetes patient registry, DPV (www.d-p-v.eu). Currently, 393 specialized diabetes clinics all over Germany and Austria enter diabetes-related data regularly and transmit the anonymized data twice a year to Ulm, Germany, for central analyses and benchmarking as described elsewhere (12,13). The DPV initiative has been approved by the Ethics Committee of Human Experimentation at Ulm University.

Insulin-treated patients with either T1D or CFRD aged >10 years at manifestation of diabetes were included in the study. As CFRD is rare in patients ≤10 years and international guidelines recommend screening for CFRD at age ≥10 years, this cut-off was used to achieve a comparable age distribution between groups. Moreover, some young CF patients have probably immunologic T1D and not CFRD. For each patient included, the most recent treatment year was analyzed. The final study population comprised 515 CFRD patients and 43,165 T1D patients.

Measurements

Insulin treatment was specified as conventional insulin therapy (CT; 1-3 injection time points/day), multiple daily insulin injections (MDI; 4-8 injection time points/day) and insulin pump therapy. Current frequency of insulin pumps was evaluated in CFRD and T1D. Demographics (e.g. age, gender, duration of diabetes, age at initiation of CSII) of pump-treated patients were analyzed. To calculate the discontinuation rate of CSII, all patients started CSII were included and followed-up.

Body mass index (BMI) and BMI standard deviation score (BMI-SDS) were used to describe nutritional status. BMI-SDS was calculated using national reference data from the KiGGS study (14); values were extrapolated for patients ≥18 years.

Though not always reliable in CFRD, hemoglobin A1c (HbA1c) was used to assess metabolic control, because it is the best measure available. To adjust for different laboratory methods, the multiple of the mean method was applied to mathematically standardize HbA1c values to the DCCT reference range (4.05–6.05%).

Severe hypoglycemia was defined as an event requiring help of another person and hypoglycemia with coma as the loss of consciousness or the occurrence of seizures.

Statistical analysis

The statistical software SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was applied for data analysis. Results are given as median with quartiles or as percentage. To compare continuous parameters, Kruskal-Wallis test was applied; for dichotomous parameters χ^2-test was used. To analyse whether there is a gender difference in pump therapy between CFRD and T1D, Cochran Mantel Haenszel test was applied. Non-parametric statistics were used because data were not normally-distributed (Kolmogorov-Smirnov test, all $p<0.01$). A two-sided $p<0.05$ was defined significant.

RESULTS

CFRD patients included in the study were younger (median [Q_1; Q_3]: 19.5 [16.8; 26.1] vs. 20.5 [16.6; 47.0] years, p<0.001), had a shorter duration of diabetes (2.7 [0.6; 5.9] vs. 5.1 [1.8; 13.5] years, p<0.001) and a lower BMI-SDS (-1.0 [-1.8; -0.2] vs. 0.5 [-0.2; 1.2], p<0.001) and HbA1c (6.8 [6.1; 8.1] vs. 7.9 [6.9; 9.3]%, p<0.001) than T1D patients. Moreover, a female preponderance was observed in CFRD (58.8 vs. 44.8%, p<0.001).

In CFRD, CT and MDI were more frequent and the use of insulin pumps was lower compared to T1D (Fig. 1, all p<0.001). Slightly more male CFRD patients had insulin pump therapy than females (4.7 vs. 3.6%, p>0.05), whereas in T1D the opposite was observed (14.9 vs. 21.2%, p<0.001). Hence, in patients with CSII, gender ratio differed between CFRD and T1D (p<0.001). Within university centers, 2.8% of CFRD patients were on CSII and 14.9% of T1D patients (p<0.001). In comparison, within private practices, 6.7% of CFRD patients had an insulin pump and 18.4% of T1D patients (p=0.001). In 60.7% of CFRD patients, pump therapy was initiated by the diabetes center documenting data in DPV. In all others, CSII was initiated by a previous health care facility, either diabetes or pneumology/gastroenterology. Rate of discontinuation of CSII was higher in CFRD than T1D (30.0 vs. 12.7%, p=0.005).

In pump-treated patients with CFRD, duration of diabetes was significantly shorter, age at manifestation of diabetes tended to be higher and age at initiation of insulin pump therapy seemed to be lower than in pump-treated patients with T1D (Table 1). None of the included CFRD patient with current use of CSII revealed a severe hypoglycemia or a hypoglycemia with coma during the recent treatment year. However, analyzing patients >5 years at diabetes manifestation, 1 CF patient had a severe hypoglycemia.Compared to CFRD patients with conventional injection regimes (CT, MDI), pump-treated CFRD patients had a significantly longer duration of diabetes and tended to be older (Table 1).

In patients who discontinued CSII, duration of diabetes seemed to be shorter in CFRD than T1D (Table 2). However, median age at initiation of CSII was comparable between groups (Table 2). In CFRD, the last HbA1c before discontinuation of CSII was in 4 patients <7%, in 3 patients between 7 and ≤8%, and in 2 patients >8%.

DISCUSSION

In diabetes care centers, insulin pump therapy was rarely used to treat adolescents and young adults with CFRD despite potential advantages. In T1D, CSII was about 4 times more common than in CFRD. Compared to T1D, CFRD patients tended to be on average 4 years younger at initiation of CSII. However, discontinuation rate of CSII was higher in CFRD than T1D.

Reasons for the low frequency of CSII in CFRD remain unclear. The lack of sufficiently large, controlled studies on the effect and safety of insulin pump therapy in CFRD may be one explanation. Compared to T1D, many CFRD patients were on a simple insulin regimen (CT). Hence, CSII may have been unwarranted in this subgroup. Furthermore, CFRD patients might be not aware of CSII as treatment modality due to less diabetes information material compared to T1D. The initiation of CSII and the care of pump-treated patients are complex and time-consuming. Pneumologists and gastroenterologists might be less familiar with CSII compared to diabetologists. Hence, insulin pumps might be less frequent in patients mostly cared for CFRD by pneumologist or gastroenterologists. The fear of a higher rate of infections or local cutaneous inflammations at the site of the cannulas due to less subcutaneous fat mass or CF-related inflammation might be another reason for withholding insulin pump therapy. Among three CFRD patients treated with CSII over two years, two mild episodes of lipohypertrophy and one of local skin infections were previously observed (11). In T1D, CSII is often initiated in toddlerhood and continued in adolescence and adulthood. In contrast, CFRD onset is later and familiarity with CSII is less pronounced than in T1D. A more economic barrier to pump use in CFRD might be the costs. However, economic implications and the accessibility to financial coverage depend on health insurance system and may differ between countries. In Germany/Austria, the government is not directly involved. Even though pump use has to be approved by insurance companies, this rarely influences the use of pumps in Germany/Austria. Nearly all children and adolescents interested receive a pump and total costs are paid by the health insurance companies.

About one third of CFRD patients discontinued insulin pump therapy. This may be explained by the rapidly change of insulin resistance. In CFRD, insulin requirement increase with infections or systemic steroid therapy and recede after improvement of health status. Improved insulin sensitivity might be the reason in 7 of our CFRD patients who discontinued CSII. The complex and time-consuming insulin pump therapy probably was no longer necessary. . In 2 of our CFRD patients who stopped CSII, non-achievement of a better metabolic control during CSII might be a factor contributing to discontinuation of insulin pump therapy as supposed by Hofer et al. (5) in pediatric and young adult T1D patients. Insulin pump therapy requires a high compliance from patients with enough time for appropriate care of the pump system and consistent diabetes control (e.g. self-monitoring of blood glucose). Hence, another simple explanation might be that patients were not able to handle insulin pump treatment beside the other CF-related therapy regimes.

In general, the few studies on CSII in CFRD revealed encouraging results. Reduction of insulin requirement and improvement of nutritional state and metabolic control were reported (7,9,11). As in our study population, no severe hypoglycemia has been documented during CSII in a CFRD patient (7-9,11). Insulin pump therapy might be an alternative to conventional injection therapy also in CFRD. Our study is the first one describing 21 pump-treated CFRD patients. However, the sample is still too small to make general statements or compare clinical data between pump-treated patients with CFRD and T1D. The missing significance for some demographic differences might be explained by the relatively low number of pump-treated CFRD patients. Even though the use of CSII is comparable between Germany and Austria (data not shown), it might differ between other countries. Hence, our data may not be directly extrapolated.

In conclusion, our analysis indicated that insulin pumps are rarely used in adolescent and young adult CFRD patients. Despite potential advantages, the reasons remain unclear. Several possible explanations are provided.

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Conflict of interest

The authors declare that there is no duality of interest relevant to this article.

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Table 1. Demographics of CFRD patients currently under insulin pump treatment compared to CFRD patients with conventional injection regimes and pump-treated T1D patients

	CFRD			T1D	
	Insulin pump	CT/MDI	p-value	Insulin pump	p-value*
Number, n	21	485	-	7,647	-
Age, yrs	22.0 [18.2; 30.1]	19.4 [16.8; 26.0]	NS	24.9 [17.3; 45.9]	NS
Male sex, %	47.6	41.2	NS	46.4	NS
Age at diabetes onset, yrs	16.0 [14.6; 19.1]	16.2 [14.0; 20.7]	NS	13.9 [11.7; 23.2]	NS
Duration of diabetes, yrs	5.8 [2.9; 9.5]	2.6 [0.6; 5.7]	0.001	7.8 [4.3; 20.4]	0.026
Age at start of insulin pump treatment, yrs	19.2 [16.5; 29.2]	-	-	23.3 [14.8; 43.5]	NS
BMI, kg/m²	20.0 [17.1; 22.4] (n=19)	19.1 [17.3; 20.9] (n=434)	NS	24.2 [21.7; 27.3] (n=7,321)	<0.001
BMI-SDS	-0.8 [-2.1; 0.3] (n=19)	-1.0 [-1.8; -0.3] (n=434)	NS	0.7 [0.0; 1.3] (n=7,321)	<0.001
HbA1c, %	7.7 [6.3; 9.6] (n=19)	6.8 [6.1; 8.0] (n=439)	0.028	7.7 [7.0; 8.7] (n=7,262)	NS

Data are given as median with quartiles or as percentage. *p-value for the comparison between pump-treated patients with CFRD or T1D. *BMI* body mass index, *BMI-SDS* body mass index standard deviation score, *CFRD* cystic fibrosis-related diabetes, *CT* conventional insulin therapy, *HbA1c* hemoglobin A1c, *MDI* multiple daily insulin injections, *NS* not significant, *T1D* type 1 diabetes mellitus, *yrs* years.

Table 2. Demographics of CFRD and T1D patients who discontinued insulin pump therapy

	Insulin pump therapy discontinued		
	CFRD	**T1D**	**p-value**
Number, n	9	1,111	-
Age, yrs	16.1 [14.9; 19.3]	17.6 [15.2; 25.1]	NS
Male sex, %	22.2	45.9	NS
Age at diabetes onset, yrs	13.4 [12.5; 14.2]	12.7 [11.2; 15.6]	NS
Duration of diabetes, yrs	1.9 [1.1; 5.3]	4.9 [2.1; 8.9]	NS
Age at start of insulin pump treatment, yrs	15.5 [14.3; 17.5]	15.8 [13.8; 23.1]	NS
BMI, kg/m²	18.4 [16.3; 20.0]	23.0 [20.5; 25.8] (n=1,088)	<0.001
BMI-SDS	-1.0 [-1.3; -0.8]	0.5 [-0.2; 1.1] (n=1,088)	<0.001
HbA1c, %	7.1 [6.7; 8.8]	8.0 [7.1; 9.2] (n=1,091)	NS

Data are given as median with quartiles or as percentage. *BMI* body mass index, *BMI-SDS* body mass index standard deviation score, *CFRD* cystic fibrosis-related diabetes, *HbA1c* hemoglobin A1c, *NS* not significant, *T1D* type 1 diabetes mellitus, *yrs* years.

Fig. 1. Current type of insulin regimen in CFRD and T1D.