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Original Article

Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study

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Aim: To evaluate the metabolic control and β-cell function 1 yr after the end of the European multicentre randomized Pediatric Onset Study.
Methods: Of 154 study patients, 131 were re-examined 24 months after type 1 diabetes onset (49.6% boys, age at onset 8.9 ± 4.3 yrs). Of which, 62 patients belonged to the primary group of the main study applying a sensor-augmented pump system during the first yr and 69 patients to the control group performing conventional insulin pump therapy with self-monitoring blood glucose. HbA1c, fasting blood glucose, and C-peptide were centrally measured (Clinical Trail Registration Number: ISRCTN05450731).
Results: At 24 months, i.e., 1 yr after the end of the interventional study, 52.4% of the patients used the sensor-augmented pump system, 46.0% conventional pump, and 1.6% multiple daily injections. HbA1c was 7.6 ± 1.3% in the primary and 7.7 ± 1.2% in the control group ($p = 0.493$). Frequent sensor use during the first yr was associated with statistically insignificant lowering of the HbA1c at 24 months ($p = 0.236$) as compared with irregular or no sensor use (7.4 ± 1.0% vs. 7.7 ± 1.3%). Although fasting C-peptide was not clearly different between the primary and control group (0.13 ± 0.17 vs. 0.09 ± 0.10 nmol/L, $p = 0.121$), patients with frequent sensor use had significantly less C-peptide loss within 24 months (C-peptide reduction 0.02 ± 0.18 vs. 0.07 ± 0.11 nmol/L, $p = 0.046$). There was no difference between the groups regarding daily insulin requirements.
Conclusion: Sensor-augmented pump therapy from onset of diabetes may lead to better long-term glycemic control and help to preserve endogenous β-cell function, if patients comply with frequent use of continuous glucose monitoring.

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Key words: children – continuous glucose monitoring – C-peptide – glycemic variability – HbA1c – sensor-augmented pump therapy

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In the European multicentre randomized Pediatric Onset Study evaluating sensor-augmented pump therapy throughout the first yr of type 1 diabetes, we found that children and adolescents with frequent use of sensors had significantly lower HbA1c values at 12 months of treatment than those with less frequent or without sensor use (1). Up to now, there is little knowledge whether initial therapy modality of the first yr of diabetes, particularly associated with continuous glucose monitoring may have a late impact on the course of the disease. Thus, the aim of the present follow-up study was to evaluate the metabolic control and β-cell function 1 yr after the end of the intervention at 24 months after diabetes onset.

Patients and methods

Briefly, in the Pediatric Onset Study 154 of 160 randomized children aged between 1 and 16 yrs with recent onset of type 1 diabetes completed the study by either receiving insulin pump treatment supported by continuous glucose monitoring (n = 76, sensor-augmented pump system Paradigm REAL-Time, Medtronic MiniMed Inc, primary group) or insulin pump therapy (MiniMed Paradigm® 515/715, Medtronic MiniMed Inc) with conventional blood glucose self-monitoring over 12 months (n = 78, control group). At the end of the study, HbA1c was not significantly different between the two groups, but patients with frequent sensor use (≥1 sensor per week) had lower HbA1c values (mean 7.1 ± 0.9%) compared to the combined group with no or low sensor usage (mean 7.6 ± 1.4%, p = 0.032) (1).

At the end of their first yr of participation in the main study, subjects were allowed to choose how they wanted to manage their diabetes (with multiple daily injections, conventional pump, or sensor-augmented pump), although this decision was tempered at some sites by the availability of health insurance coverage for the equipment and consumables. Patients of the control group were offered to use the sensor-augmented pump system free of charge for 3 months if they wanted.

According to the study protocol, a voluntary late follow-up visit at 24 months after diabetes onset was offered to all study patients including a minimal invasive procedure, i.e., measurement of HbA1c as well as blood glucose and C-peptide levels at fasting conditions. Continuous glucose monitoring was not performed.

Of 154 study patients (85.5% follow-up compliance), 131 were re-examined. There were 65 boys and 66 girls with a mean age at diabetes onset of 8.9 ± 4.3 yrs. Of the 131 patients, 62 belonged to the primary interventional group with sensor-augmented pump treatment (N = 76) and 69 to the control group of the main study (N = 78). There were no differences between groups concerning age (p = 0.670), gender (p = 0.789), or body mass index (BMI, p = 0.765) distribution. Clinical and treatment data of the second yr were available in 124 of the 131 subjects. HbA1c, fasting blood glucose, and C-peptide values were centrally measured at the LKF-Laboratorium für Klinische Forschung, Kiel, Germany in all 131 patients.

Results

During the second yr, all 58 clinically documented patients from the primary group continued with sensor-augmented pump therapy. At the 24-month follow-up visit, a total of 65 patients (58 primary group and 7 controls) used the sensor-augmented pump system (52.4%), whereas 57 patients from the control group had continued with conventional insulin pump therapy (46.0%) and two control group patients had switched to multiple daily injections (1.6%).

HbA1c was 7.6 ± 1.3% in the 62 patients of the primary and 7.7 ± 1.2% in the 69 patients of the control group (p = 0.493). About 48.8% of patients had HbA1c below 7.5% with no siginificant difference (p = 0.436) between the primary and control group (52.5% vs. 45.6%). Frequent sensor use (≥1 sensor per week, N = 33) during the first yr of diabetes was associated with insignificantly lower HbA1c values at 24 months as compared with irregular or even no sensor use (7.4 ± 1.0% vs. 7.7 ± 1.3%, p = 0.236) (Fig. 1).

Daily insulin requirements at follow-up (0.79 ± 0.26 vs. 0.71 ± 0.19 units per kg body weight, p = 0.067) and frequency of blood glucose self-monitoring (6.0 ± 2.1 vs. 6.1 ± 1.6 measurements per day, p = 0.823) did not differ between the primary and control group, respectively.

Although fasting C-peptide at follow-up was not significantly different between the primary and control group (0.13 ± 0.17 vs. 0.09 ± 0.10 nmol/L, p = 0.121), patients with frequent sensor use during the first yr of diabetes (≥1 sensor per week) had significantly less C-peptide loss within 24 months. C-peptide reduction was 0.02 ± 0.18 nmol/L in patients with frequent sensor use compared with 0.07 ± 0.11 nmol/L in those with irregular or even no sensor use (p = 0.046) corresponding with 24-month C-peptide values of 0.14 ± 0.17 nmol/L and 0.09 ± 0.13 nmol/L, respectively, and relative C-peptide loss of 30.0 and 41.3% within the second yr. The relative decrease of C-peptide between onset and follow-up at 12 and 24 months in these both groups (p = 0.005) is presented in Fig. 2.

In multiple linear regression analysis, the frequency of sensor use was the only significant parameter, which was independently associated with the relative C-peptide change over 24 months (p = 0.033) apart

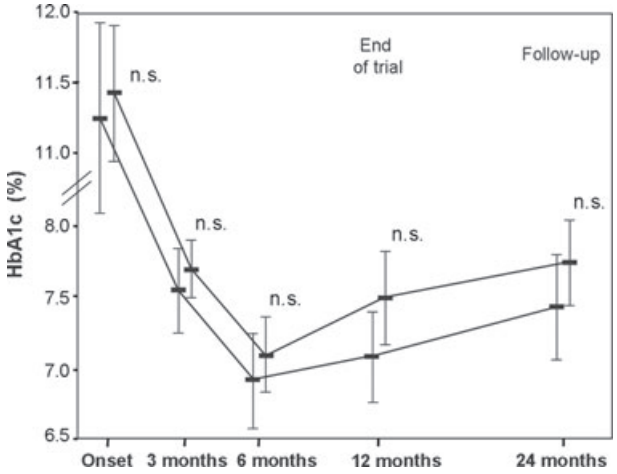

Fig. 1. HbA1c up to 24 months from onset of diabetes in patients with frequent sensor use of at least one sensor per week during the first yr of diabetes (lower curve) and in those with no or low sensor use during the first yr of diabetes (upper curve). Values are given as mean ± 2 standard error of the mean. n.s., not significant.

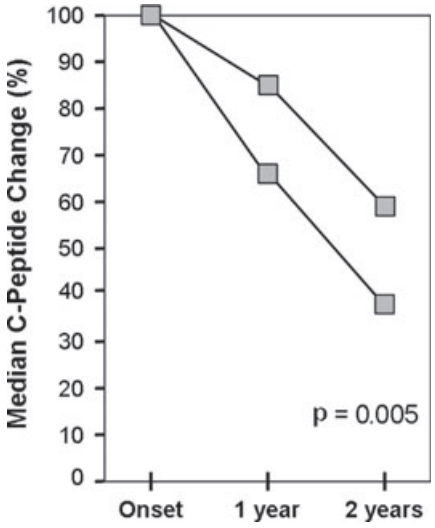

Fig. 2. Relative change of fasting C-peptide from onset up to 24 months of diabetes in patients with frequent sensor use of at least one sensor per week during the first yr of diabetes (upper curve, relative decrease 15.0 and 40.5% at 1 and 2 yrs, respectively) and in those with no or low sensor use during the first year of diabetes (lower curve, relative decrease 34.9 and 61.8% at 1 and 2 yrs, respectively).

from age at onset ($p = 0.226$), BMI ($p = 0.141$), and glycemic variability (MAGE, $p = 0.403$).

During the recent follow-up period, two episodes of diabetic ketoacidosis and one episode of severe hypoglycemia occurred in the control group within the second yr of diabetes.

Discussion

By the findings of the follow-up study, the results of the main study in patients treated with insulin pump from the beginning of their disease have been confirmed and extended. We observed that the frequent use of sensors during the first yr of diabetes was associated with smaller loss of β-cell function up to 24 months of the disease. Although, in the total study group, endogenous insulin production decreased over 24 months, the loss of fasting C-peptide (52.7%) was lower than expected. In a recent publication including data from 5845 patients with type 1 diabetes, Pozzilli et al. reported from a 70 to 60% reduction of the fasting C-peptide levels over 24 months in patients aged 0–11 yrs and 12–1 yrs at diabetes onset, respectively (2). The potential benefit of higher levels of C-peptide during the course of type 1 diabetes has been demonstrated in the longitudinal data analysis in patients participated in the Diabetes Control and Complications Trial (DCCT). Even modest levels of β-cell activity at entry in the DCCT were associated with reduced incidences of retinopathy and nephropathy during the follow-up (3). Moreover, continuing C-peptide secretion was associated with less frequency of severe hypoglycemia, which is the major complication of intensive diabetic therapy.

In the follow-up study cohort, glycemic values after 12 months of diabetes (7.4 ± 1.3%) were lower than previously reported for comparable pediatric populations (4) and maintained at low level after 2 yrs of diabetes (7.6 ± 1.2%). A slight HbA1c increase during the second yr of diabetes is associated with the natural course of the disease and maybe partially influenced by the decreased use of sensors after the end of the main study, although the sensor use in the second yr was not recorded. Furthermore, HbA1c in the interventional group tends to rise after the intervention of the study ends, and the control and study populations come closer to having the same HbA1c. This may be common to all studies of this nature where intensive management of the study group ends (e.g. DCCT (5)).

In conclusion, sensor-augmented pump therapy from onset of type 1 diabetes may lead to better long-term glycemic control and help to perserve endogenous β-cell function if patients comply with frequent use of continuous glucose monitoring.

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