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Insulin Requirements in Relation to Insulin Pump Indications in Type 1 Diabetes

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Abstract

The purpose of the current research was to assess changes in daily insulin requirements in type 1 diabetic patients transitioning from multiple daily injections (MDI) of insulin to continuous subcutaneous insulin infusion (CSII) using an external insulin pump, according to clinical indications for changing therapy. The charts of 70 patients with type 1 diabetes (T1D) initiating insulin pump therapy were retrospectively reviewed before CSII and after optimization of glycaemic profile with CSII during hospital admission. Daily insulin doses, basal/bolus distributions, dose changes during treatment transition and glycaemic outcomes with MDI and optimized CSII according to insulin pump indications were evaluated. Daily insulin doses were not significantly different among indication groups, with both MDI and CSII; likewise, the overall daily distribution of basal/rapid insulin ratio was similar, around 40/60. With optimized CSII, significant differences were found only in basal/bolus distribution in patients initiating CSII for recurrent hypoglycemia, who had a significantly lower basal (6.4% lower) and a complementary higher bolus requirement, compared to patients initiating CSII for HbA1c ≥ 8.5%. At transition, basal insulin needs declined similarly in the high HbA1c and impractical/inflexible MDI groups by approximately 20%, and up to 30% in the recurrent hypoglycaemia group; bolus doses decreased by 20% when the indication was high HbA1c and by approximately 15% for the other indications. Glycaemic control was significantly improved only in patients initiating CSII for high HbA1c (≥8.5%). Insulin pump indication should be considered when starting T1D patients on CSII. These findings may support clinicians in decision making regarding insulin dose changes when initiating insulin pump therapy.

Keywords: basal rate, insulin dose, insulin infusion systems, external infusion pump, glycated haemoglobin

Introduction

The use of continuous subcutaneous insulin infusion (CSII) through an external insulin pump has been proven to be safe and effective in the treatment of type 1 diabetes (T1D), several studies demonstrated its superiority over multiple daily injections (MDI) therapy, in terms of glycaemic control, glucose variability, rate of hypoglycemia and quality of life (Jeitler *et al.*, 2008; Pickup and Renard, 2008; Fatourechi *et al.*, 2009; Bragd *et al.*, 2010; Gimenez *et al.*, 2010). Although insulin pump use has increased considerably in the past decades in the developed countries, it is still underused in developing regions, due to the cost burden for healthcare systems. Nevertheless, the transition from MDI to CSII is not clearly defined by guidelines and optimization of glycaemic control is often delayed, as insulin dose adjustments are required (Bode *et al.*, 2002; Conrad *et al.*, 2002).

When switching adults to CSII, the general recommendation is to reduce the MDI total daily dose by up to 25% (Bode, 2013), while in children, the pediatric consensus proposes a decrease in total pre-pump insulin dose by 10-20% (Phillip *et al.*, 2007). Basically, different clinical trials reporting insulin dose changes in T1D patients transitioning from MDI to CSII, found either a higher reduction (30-36%) (Ahern *et al.*, 2002; Doyle *et al.*, 2004), or no change in daily insulin requirements (Litton *et al.*, 2002). Moreover, the basal and bolus insulin requirements have been reported to differ significantly in pediatric patients and adults, although basal/bolus ratio established for adults (50/50) is usually also applied for children (Cemeroglu *et al.*, 2013).

It is well known that insulin requirement depends on many factors, such as age, duration of diabetes, physical activity, time of day, etc (Chico *et al.*, 2014). However,

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literature data regarding insulin dose changes when transitioning from MDI to CSII for different insulin pump indications are scarce. Identifying these changes for subgroups of type 1 patients could be helpful in attaining a faster optimization of blood glucose levels, to reach the desired HbA1c target.

The main objective of this study was to evaluate the changes in total, basal and bolus insulin requirements when switching T1D patients from MDI to CSII for different clinical reasons.

Material and Methods

Selection and description of participants

Medical records from type 1 diabetic patients transitioning from multiple daily injections to insulin pump therapy during hospital admission at the Clinical Center of Diabetes, Nutrition and Metabolic Diseases, Cluj-Napoca, Romania, between January 2002 and December 2011 were retrospectively analyzed. Inclusion criteria consisted of: T1D patients with at least one year diabetes duration and experience with MDI ($\geq$ 4 insulin injections/day) and self-monitored blood glucose (SMBG) (for at least 4 times/day); patients fulfilling the criteria of the national insulin pump program of the Ministry of Health for a fully reimbursed permanent insulin pump and infusion sets: children and adults with T1D and failure of MDI treatment; T1D and pregnant women (Romanian National Insurance House, 2015) were referred from across different diabetes care settings throughout the country to the Diabetes Center in Cluj-Napoca to be hospitalized and started on an insulin pump.

Patients admitted in the Romanian national insulin pump program for T1D were divided into 3 groups according to the main indications for insulin pump therapy recommended by international diabetes professional societies: high HbA1c $\geq$ 8.5% with MDI therapy, MDI treatment inappropriate or impractical or recurrent hypoglycaemia on MDI (Phillip *et al.*, 2007; Pickup, 2012a; Grunberger *et al.*, 2014). Exclusion criteria: pregnancy, medications affecting glucose levels (e.g. glucocorticoids) and other chronic comorbidities. Data were retrospectively collected during pre-pump MDI and with CSII after achieving a favourable glycaemic profile before hospital discharge.

Ethical issues

The study was conducted in accordance with the ethical principles for medical research involving human subjects stated in the revised Helsinki Declaration.

Methods

All patients scheduled to initiate CSII treatment have been admitted in the diabetes clinic for at least one week and enrolled in an intensive educational program for people beginning CSII, conducted by experienced diabetes specialists and diabetes educator nurses. Demographic, anthropometric and diabetes specific data were recorded.

Technical information

Long acting insulin analogs were stopped 24 h before the planned CSII initiation, and NPH insulin was used for overnight glycaemic control. Pumps used were: Accu-Check Spirit, Paradigm RT, Veo, Minimed 508 and all pumps were started on rapid-acting insulin analog.

Pre-pump total daily dose (TDD) was reduced by 20 $\pm$ 5%; 50% of this amount was used as basal rate in adults and 40% in children, and most patients started on the same hourly basal rate, except for night time hourly basal rate from 12:00 AM to 3:00 AM, which was 0.1 U/h lower or higher than the 3:00 AM-7:00 AM interval, depending on individual tendencies for night time hypoglycaemia; also, daytime hypoglycaemia-prone time intervals were covered by 0.1 U/h lower insulin doses. Basal rate adjustments were made based on 6 h fasting tests performed at successive time intervals, skipping one meal/day on separate days, during hospital admission. Daily adjustments of the basal rate were made according to hourly SMBG during daytime fasting tests and bedtime, respectively 3 AM and 7 AM blood glucose for the night time basal rate. If fasting was not possible (e.g. children), the 2 h postprandial and the next pre-meal values were considered for basal rate adjustment. An HbA1c target $\leq$ 7.5% was considered reasonable for all patients.

Statistics

Statistical analysis was performed using SPSS Statistics v.22 (IBM Corporation). Normal distribution of variable was tested using the Shapiro-Wilk test. Continuous data were expressed as mean $\pm$ standard deviation and categorical variables as percentages. Student's t test was used to compare quantitative variables that proved to be normally distributed. Groups were compared by one-way analysis of variance (ANOVA). Non-parametric tests were used to compare variables that proved not to have a normal distribution. Correlation between variables was assessed using Pearson's correlation analysis. Statistical significance was defined as p < 0.05 when two groups were compared and p < 0.0167 when three groups were compared.

Results

A total of 70 T1D patients were included in the study: mean age was 19.1 $\pm$ 8.9 years, while mean diabetes duration at pump start was 7.7 $\pm$ 5.7 years, 40% male and 88.5%, from urban area. The proportions of patients on pre-pump basal insulin analog and rapid-acting analog were 92.8% and 98.5%, respectively.

Patient distribution according to insulin pump indications was the following: Group 1 -high HbA1c $\geq$ 8.5% with MDI therapy - 50% (35 patients) of cases, Group 2 - MDI treatment inappropriate or impractical, meaning 34.3% (24 patients) and Group 3 - recurrent hypoglycaemia on MDI, representing 15.7% (11 patients). Patient baseline characteristics and MDI insulin requirements organized by insulin pump indications are presented in Table 1.

Kruskal-Wallis tests conducted to determine if there were differences in age or diabetes duration between the three groups, showed no significant differences (p = 0.74 and 0.76, respectively).

There were no significant differences in body mass index between the three groups (Kruskal-Wallis test, p = 0.202). A higher percentage of females was recommended to start on insulin pump for high HbA1c (62.9%) or recurrent hypoglycaemia (63.6%).

Baseline MDI HbA1c across the three different insulin pump indication classes was significantly different among the groups with ANOVA testing (p < 0.0005), HbA1c decreasing

Table 1. Patient baseline characteristics and MDI insulin doses according to insulin pump indication

	Insulin pump indication		
	High HbA1c ≥ 8.5% with MDI	MDI inappropriate/impractical	Recurrent hypoglycaemia on MDI
N	35	24	11
Age (years)	19.5 ± 9.7	19.4 ± 8.1	17.4 ± 9
Male (%)	37.1	45.8	36.4
Diabetes duration (years)	7.9 ± 5.1	7.4 ± 5.1	8.2 ± 8.5
Weight (kg)	56.5 ± 19.1	53.8 ± 12.7	48.8 ± 15.7
Height (m)	1.6 ± 0.1	1.6 ± 0.1	1.5 ± 0.1
BMI (kg m^{-2})	21.2 ± 4.7	20.3 ± 3.5	18.7 ± 2.3
MDI HbA1c (%)	9.6 ± 1.0	7.7 ± 0.4	6.6 ± 0.3
MDI total daily dose (U)	45.7 ± 15.3	46.1 ± 16.7	40.9 ± 16.9
MDI TDD (U kg^{-1})	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
MDI bolus U kg^{-1}	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
MDI basal U kg^{-1}	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.7
MDI bolus/TDD (%)	58.2 ± 9.3	58.7 ± 11.2	59.4 ± 9.6
MDI basal/TDD (%)	41.8 ± 9.3	41.2 ± 11.2	40.5 ± 9.6

Data are presented as mean ± standard deviation, unless otherwise stated. BMI- body mass index; TDD- total daily dose; MDI- multiple daily injections

Table 2. CSII insulin doses according to insulin pump indication

	Insulin pump indication		
	Group 1	Group 2	Group 3
CSII total daily dose (U)	33.8 ± 8.4	35.7 ± 8.7	30.9 ± 12.4
CSII total daily dose (U kg^{-1})	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.2
CSII bolus U kg^{-1}	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
CSII basal U kg^{-1}	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
CSII bolus/TDD (%)	57.5 ± 6.8	60.9 ± 8.8	63.9 ± 3.8
CSII basal/TDD (%)	42.5 ± 6.8	39.1 ± 8.8	36.1 ± 3.8

Data are presented as mean ± standard deviation, unless otherwise stated. TDD- total daily dose; CSII- continuous subcutaneous insulin infusion

significantly from Group 1, to Group 2, to Group 3. Homogeneity of variances using Levene's test was violated. Games-Howell post-hoc analysis revealed that HbA1c decreased significantly ($p < 0.0005$) from Group 1 to Group 2 (-1.8; 95% CI (-2.3 to -1.3)), as well as from Group 1 to Group 3 (-2.9; 95% CI (-3.4 to -2.5); $p < 0.0005$).

Pre-pump insulin dose differences among pump indication groups

No statistically significant differences (ANOVA, $p > 0.05$) were found between the three groups regarding MDI doses (rapid, basal and total daily doses) used before starting on insulin pump. MDI insulin dose requirements are presented in Table 1.

Basal insulin requirement in the whole study group accounted for 41.4 ± 9.9% of MDI daily totals.

Insulin pump dose differences among pump indication groups

CSII doses reached during adjustment to achieve a favourable glycaemic profile, according to insulin pump indication groups, are represented in Table 2.

There were no statistical differences between the three groups with regards to CSII total, bolus and basal insulin doses (U kg^{-1}), except for basal/bolus ratios, which were significantly different among the groups. Basal requirement in the whole study group accounted for 40.3 ± 7.5% of pump daily totals.

Basal insulin percentages across groups decreased from Group 1 to Group 2, to Group 3 (ANOVA), and the Games-Howell post-hoc analysis showed a significant decrease in basal insulin percentage ($p = 0.001$) from Group 1 to Group 3 (6.4%; 95% CI (2.4 to 10.4)), and an equivalent significant increase in bolus percentage from Group 1 to Group 3.

Insulin dose changes after transition from MDI to CSII according to indication

There was a strong positive correlation (Pearson correlations) between MDI and CSII total daily insulin doses ($r = 0.696$, $p < 0.0005$) (U kg-1), bolus ($r = 0.589$, $p < 0.0005$) (U kg^{-1}) and basal ($r = 0.582$, $p < 0.0005$) insulin (U kg^{-1}) needed. Linear regression analysis established that each of the pre-pump insulin doses (total, basal and prandial insulin doses) could statistically predict CSII corresponding insulin doses; pre-pump total, basal and prandial requirements accounted for 47.7%, 32.9% and 33.7% of the explained variability in CSII total, basal and prandial insulin doses, respectively.

All insulin requirements decreased when transitioning from MDI to CSII: total daily insulin dose/kg decreased to 78.3 ± 15.6%, bolus/kg/day decreased to 82.2 ± 23.7% and basal/kg/day decreased to 79.4 ± 26.4% of the previous MDI doses, with no significant differences among the indication groups.

When indication groups were analyzed separately, paired samples t-tests indicated statistically significant reductions in all insulin requirements when transitioning from MDI to insulin pump (Fig. 1); overall mean reductions of 0.19 ((95% CI, 0.091 to 0.180) U kg^{-1}, $p < 0.0005$) in total daily dose, of 0.08 ((95% CI, 0.091 to 0.10) U kg-1, $p < 0.0005$) in basal and of 0.10 ((95% CI, 0.06 to 0.10) U kg^{-1}, $p < 0.0005$) in bolus requirements were found.

HbA1c at 3 months and insulin pump indications

Median HbA1c values achieved at 3 months were the highest in Group 1 (8.0%; IQR (interquartile range) 7.0-9.0), while the lower values were in Group 3 (6.6%, IQR 5.8-7.4) and 7.6%, IQR 6.8-8.4 in Group 2.
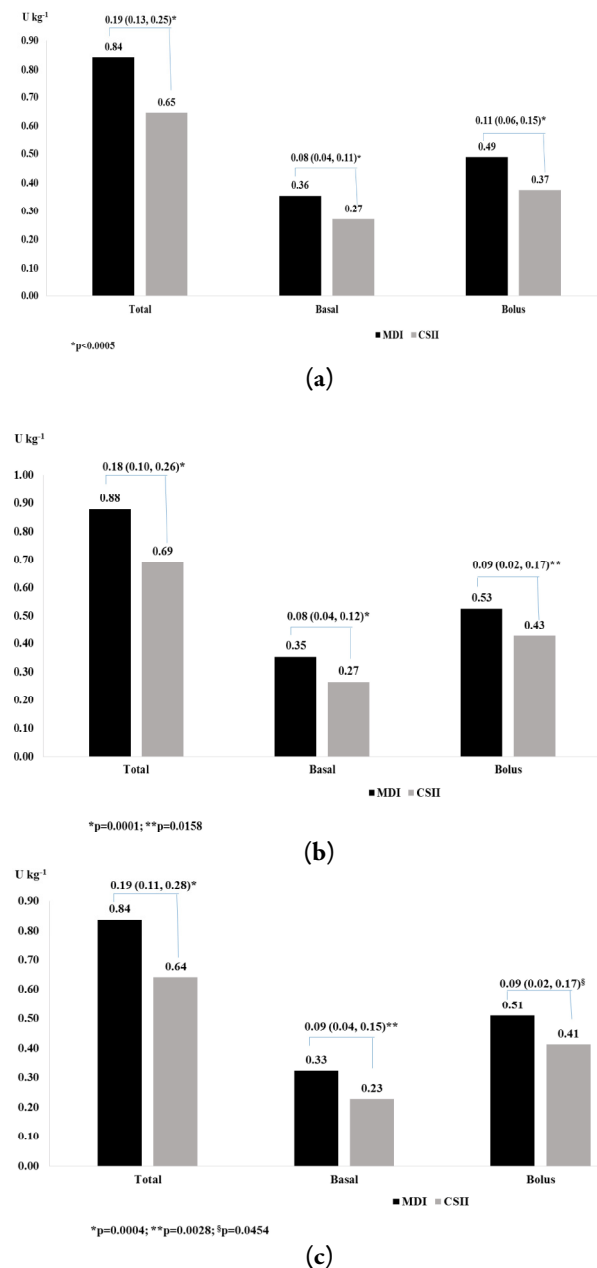
(a)

(b)

(c)

Fig. 1(a) MDI to CSII insulin dose change in patients with high HbA1c ≥ 8.5% pump indication; (b) MDI to CSII insulin dose change in patients with inappropriate/ impractical MDI insulin pump indication; (c) MDI to CSII insulin dose change in patients with recurrent hypoglycaemia insulin pump indication; p values according to paired t-test

A Kruskal-Wallis test was conducted to determine if there were differences in HbA1c values achieved at 3 months between groups that differed in their insulin pump indication, considering that the basal rate did not vary more than 5%. Distributions of HbA1c values were not similar for all groups, as assessed by visual inspection of boxplots. The distributions of HbA1c values were statistically significantly different between the indication groups, χ^2 (2) = 22.842, p < 0.0005.

Subsequently, pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. This post hoc analysis revealed statistically significant differences in HbA1c values between Group 3 (mean rank = 11.73) and Group 2 (mean rank = 32.83), (p = 0.013), and respectively between Group 3 and Group 1(mean rank = 44.80), (p < 0.0005), but not between Group 1 and Group 2.

Patients in Group 1 experienced a significant reduction in median HbA1c value (1% reduction), after the initiation of insulin pump therapy at 3 months (8%) versus baseline (9.2%), as assessed by Wilcoxon signed-rank test (p < 0.0005). No statistically significant reductions in HbA1c were found in the other treatment indication groups.

Discussion

The hereby retrospective study described three groups of young T1D patients transitioning from MDI to insulin pump therapy for different indications. The most frequent reason for changing treatment was the high HbA1c (in half of the patients under study), followed by the inappropriate/impractical use of MDI (34.3%).

During MDI treatment, no differences in daily insulin doses were found among groups; the basal/bolus ratios used during MDI in the three groups were similar among indications.

After switching to CSII and optimizing insulin profile, there were still no significant differences among the indication groups with regards to total, basal and bolus insulin requirements. The basal rate totalled about 42% of daily dose in the high HbA1c patients, and was lower in the other two indication groups. However, significant differences were found only in basal/bolus distribution for patients initiating CSII for recurrent hypoglycaemia, who had a significantly lower basal (6.4% lower) and a complementary higher bolus requirement, compared to patients initiating CSII for high HbA1c. The rapid/basal insulin ratios found in the young population under study was in line with findings from other studies in prepubertal, peripubertal and postpubertal patients, the basal insulin percentage rarely reaching the adult level of 50%, and usually ranging from 30-45% in these age groups (Conrad *et al.*, 2002; Danne *et al.*, 2006; Phillip *et al.*, 2007; King, 2010; Cemeroglu *et al.*, 2013).

Switching patients from MDI to CSII led to a total daily insulin dose decrease of 22%; basal insulin requirements declined similarly in the high HbA1c and impractical/inflexible MDI groups by approximately 20%, and slightly higher, up to 30%, in the recurrent hypoglycaemia group; bolus doses decreased by 20% when the indication was high HbA1c and by approximately 15% for the other indications. All insulin requirements decreased significantly with CSII versus MDI. These findings are similar to the study conducted by Nicolajsen (2012) in a somewhat younger age group, 13.1 ± 3.9 years, also studied for different pump indications.

After all insulin dose adjustments with CSII and optimization of glycaemic control in all indication groups, the glycaemic outcomes at 3 months post-transition to CSII were significantly better in the high HbA1c indication group (1% HbA1c reduction) versus the other two clinical indications, which was in agreement with the results published by other studies. Both meta-regression of mean HbA1c levels from conducted trials and data from individual patients showed that the greatest reduction in HbA1c levels with CSII occurred in

those patients with the highest HbA1c level on MDI at baseline. There is the assumption that when quality of life improvements are taken into account along with reductions in HbA1c level, CSII is cost-effective when HbA1c levels on MDI are ≥ 8.5% (Pickup, 2012b).

Conclusions

When transitioning from MDI to CSII, insulin pump indication has to be considered in order to enhance pump bolus/basal insulin distributions in pre, peri and postpubertal T1D patients. This may be useful in reshuffling daily insulin requirements directly to optimized patient needs when transitioning to an insulin pump in clinical practice. Results from the present study support that the best outcomes are in patients initiating CSII for a high HbA1c indication.

The main limitations of the current study are related to the retrospective nature of the observation, as well as to the small number of patients included in the CSII indication groups.

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