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Treatment and long-term follow-up of patients diagnosed with type 1 diabetes mellitus before age 5

Abstract

Objectives: This study aimed to determine the effects of continuous subcutaneous insulin infusion (CSII) treatment on anthropometric measurements, mean HbA1c, and insulin dosage in patients diagnosed under 5 years of age and compare with multiple-dose injection therapy (MDI).
Methods: Children with type 1 diabetes mellitus, diagnosed <5 years since 2000 and their 19-year follow-up were evaluated retrospectively. Weight, height, body mass index (BMI), blood pressure, and HbA1c values were recorded for each visit.
Results: Hundred and five patients (58.1% female, 41.9% male) were included in the study. Sixty-three (60 %) patients were treated by CSII and 42 (40%) by MDI. Mean age at diagnosis was 2.68 ± 1.42 and 3.29 ± 1.30 years respectively. Mean follow-up was 7.42 ± 4.76 and 6.01 ± 4.41 years respectively. For each group, weight standard deviation score (SDS) increased significantly in the first year after the diagnosis (p<0.001), and with the onset of puberty weight SDS decreased significantly (p<0.001). The trend of weight and BMI SDS changes over the years showed similar characteristics in both groups. During follow-up height SDS was similar in both groups except in Tanner stage 5. When puberty was completed, mean height SDS was 0.51 ± 1.03 in CSII and −0.31 ± 0.75 in the MDI group (p: 0.029). Mean HbA1c was significantly lower in the CSII group (7.62 ± 0.82 and 8.17 ± 1.22 respectively). Systolic and diastolic blood pressure change trends during the follow-up were also similar in both groups.
Conclusions: CSII treatment had positive effects on metabolic control and height SDS in patients with early-onset diabetes without increasing BMI.

Keywords: height; insulin pump; metabolic control; preschool type 1 diabetes.

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases affecting more than one million children and adolescents globally [1, 2]. There is a worldwide increase in the incidence of T1DM, especially in young children under the age of 6 years old [3, 4]. In this age group, unpredictable feeding, inconsistent physical activity, parent-dependent eating habits, living with diabetes during the whole pubertal period complicate diabetes management and make it difficult to achieve good metabolic control [5–8]. Recurrent episodes of hypoglycemia, especially at young ages, may cause short- and long-term adverse effects on cognitive function [7]. Impaired growth is a well-documented other complication of diabetes; studies suggest that good metabolic control is crucial for normal growth [7, 8]. Continuous subcutaneous insulin infusion (CSII) therapy reduces HbA1c and complication rates without increasing severe hypoglycemia. Considering all these data, CSII therapy is the preferred method of insulin administration for young children (aged<7 years) with T1DM [9]. This study aims to compare metabolic control, to assess growth parameters and frequency of diabetic ketoacidosis (DKA), hospitalization and complications within two treatment modalities during follow-up.

Materials and methods

This is a single-center retrospective study, designed in pediatric T1DM patients who were diagnosed before 5 years of age. Patients who applied to a university hospital between 2000 and 2019, who

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were diagnosed with T1DM according to International Society of Pediatric and Adolescent Diabetes/International Diabetes Federation (ISPAD/IDF) guidelines [10], were included. Patients were excluded if they had other underlying conditions that could affect glycemic control and growth such as uncontrolled thyroid disease, steroid usage, and whose medical records were insufficient. Clinical and laboratory findings, weight, height, Tanner stage, as well as complete follow-up data were gathered retrospectively from patients' files.

Standing height was measured to the nearest millimeter using a SECA264 stadiometer, weight was measured using an electronic scale to the nearest 100 g. Height, weight, and BMI were converted to Z scores using Turkish children references [11]. Blood pressure was measured with a standard sphygmomanometer and appropriate pediatric cuff. All auxological parameters and blood pressure standard deviation scores were calculated by a computer program for Turkish children [12]. CSII was initiated by a training program by a specialist nurse and a pediatric endocrinologist. Carbohydrate counting was given by a specialist dietician for patients (if age was appropriate) and caregivers, minimum 3 months before CSII application. On the other hand, while carbohydrate counting, education was given simultaneously if the family prefers CSII treatment at the time of diagnosis. MDI protocol was applied as long-acting and short-acting insulin 4–5 times a day (glargine/detemir and aspart/glulisine/lispro). Insulin (units/kg/day) was calculated at each visit for all patients. Upon transfer to adult clinics, diabetic patients were examined routinely and HbA1c was measured during 3 months of intervals. For the study group, all necessary information up to the end of 2019 was recorded from patients' archive files. For girls, the first detection of the breast budding, for boys first detection of 4 mL testis volume were accepted as Tanner stage 2. For girls, menarche date and for boys, testis volume 20–25 mL were accepted as Tanner stage 5.

DKA was diagnosed according to the International Society of Pediatric and Adolescent Diabetes/International Diabetes Federation (ISPAD/IDF) guidelines [13]. The target HbA1c of the clinic was 7.5% (ISPAD). HbA1c levels were obtained from the clinical medical records and annual mean HbA1c was calculated. HbA1c was measured by turbidimetric inhibition immunoassay (Roche Cobas c513 analyzer using the Tina quant® HbA1c Gen. 3 assay, Germany). The study was approved by the Ege University Medical Ethics Committee (approval number: 20-1.1T/57). Written, informed consent was obtained from all participants and their parents.

Statistical analysis

Categorical data were described using observed frequencies and percentages, and continuous variables were summarized by their means and standard deviations (or medians and interquartile ranges in case of serious deviations from normality) with a statistical package (SPSS Inc., version 21.0, Chicago, IL, USA). Nonparametric Brunner and Langer model (F1-LD-F2) was used to testing group effects by using web-based software (R software, version 3.3.1, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org). In the method, the hypotheses are formulated in terms of distribution functions of experimental factors, and the effect of these factors is estimated by relative marginal effects. Also, Wald-type and analysis of variance (ANOVA)-type test statistics are used in this nonparametric model. In all studies, p values <0.05 were considered to be statistically significant.

Results

After the first evaluation for eligibility data, 105 patients out of 141 were appropriate for the study group. Sixty-one (58.1%) of patients were female and 44 (41.9%) were male. A total of 63 (60%) patients were treated by CSII and 42 (40%) by MDI. CSII was initiated mean 2.41 ± 0.33 years after diagnosis. In 10 patients, CSII was initiated at the time of diagnosis.

Fifty-five patients were on MiniMed® Paradigm® VEO, eight patients on Medtronic Minimed® 640G®, and during follow-up, 12 patients changed from MiniMed® Paradigm® VEO to 640G®. Twenty-six patients were using continuous glucose monitoring (CGM) with pump therapy (Sensor augmented pump), nine of them were using Paradigm® VEO pump with low glucose suspend function, 17 patients were using 640G® pumps with predictive low glucose suspend function. No patient was using a sensor in the MDI group.

Mean age at diagnosis in CSII and MDI group was 2.68 ± 1.42 and 3.29 ± 1.30 years (p: 0.025), the mean duration of T1DM was 7.42 ± 4.76 and 6.01 ± 4.41 years, respectively. Sixty-six (62.8%) patients were admitted at the time of diagnosis and 39 (37.2%) patients for follow-up.

In the MDI group, 28 (66%) patients performed carbohydrate counting, while 14 (34%) patients deemed unsuitable or unwilling for carbohydrate counting and performed an exchange nutrition plan.

At the time of diagnosis, mean weight standart deviation score (SDS) and height SDS were: −0.24 ± 1.14 and −0.16 ± 1.1 respectively for all the study groups (Table 1). During follow-up, in the first year after the diagnosis, weight SDS change was 0.3 ± 0.95 SD and increased significantly (p<0.001). The change in weight SDS in the follow-up period was not different between CSII and MDI groups (p: 0.90).

In the whole study group, mean BMI SDS at the time of diagnosis was −0.09 ± 1.25 and increased significantly to 0.62 ± 0.96 in the first year of follow-up. With puberty, BMI SDS decreased to −0.10 ± 1.07 (p<0.001), and it was preserved till puberty was completed (−0.07 ± 1.2). Changes in BMI SDS in the follow-up period were not different between CSII and MDI groups (p: 0.58) and in between sensor augmented pump (SAP) and standard pump groups (p: 0.64).

Table 1: Auxologic measurements of patients as mean ± SD.

		n	Age, year	Weight SDS	Height SDS	BMI SDS
Diagnosis	CSII	44	2.68 ± 1.42	−0.16 ± 1.23	−0.12 ± 0.96	0.01 ± 1.24
	MDI	26	3.29 ± 1.3	−0.37 ± 0.99	−0.22 ± 1.13	−0.25 ± 1.28
p-Value				0.491	0.885	0.377
First year	CSII	50	3.75 ± 1.43	0.4 ± 1.07	−0.15 ± 1.09	**0.75 ± 0.97**
	MDI	31	4.36 ± 1.28	0.15 ± 0.72	−0.23 ± 0.93	**0.41 ± 0.92**
p-Value				0.242	0.773	**0.043**
Second year	CSII	49	4.69 ± 1.41	0.41 ± 0.98	−0.16 ± 1.08	0.68 ± 0.99
	MDI	29	5.24 ± 1.36	0.30 ± 0.89	−0.09 ± 0.84	0.46 ± 0.96
p-Value				0.629	0.770	0.364
Fifth year	CSII	40	7.79 ± 1.45	0.34 ± 1.17	0.26 ± 1.2	0.29 ± 1.14
	MDI	24	8.03 ± 1.36	0.26 ± 0.92	0.04 ± 0.93	0.19 ± 0.86
p-Value				0.774	0.448	0.716
Tanner 2	CSII	33	10.2 ± 1.1	0.03 ± 1.1	0.01 ± 1.16	−0.03 ± 1.08
	MDI	14	10.7 ± 1.21	−0.32 ± 1.02	−0.25 ± 0.84	−0.28 ± 1.06
p-Value				0.298	0.447	0.728
Tanner 5	CSII	21	13.29 ± 1.48	0.1 ± 1.21	**0.51 ± 1.03**	−0.08 ± 1.09
	MDI	9	14.1 ± 0.98	−0.18 ± 1.53	**−0.31 ± 0.75**	−0.06 ± 1.51
p-Value				0.585	**0.029**	0.972

CSII, continuous subcutaneous insulin infusion; MDI, multiple dose injection; SDS, standard deviation score; BMI, body mass index. Bold values in the table are significant p values.

Three (4.8%) patients in the CSII group and two (4.8%) patients in the MDI group were obese on the last outpatient visit data according to WHO criteria [14].

Mean height SDS was −0.22 ± 1.13 at the time of diagnosis (Figure 1) and till Tanner stage 5, there was no difference between CSII and MDI groups, but in Tanner stage 5 (n: 30), mean height SDS was 0.51 ± 1.03 in CSII and −0.31 ± 0.75 in the MDI group (p: 0.029). Target height SDSs of CSII and MDI groups were similar, −0.25 ± 0.7 and −0.25 ± 0.97, respectively (p: 0.982).

Systolic and diastolic blood pressure SDSs over the years between CSII and MDI groups were similar (p: 0.29 and 0.38, respectively).

The mean HbA1c value at the end of the first year was 7.37 ± 0.78% in CSII and 7.33 ± 0.81% in the MDI group (p: 0.07). Mean HBA1c was significantly lower in the CSII group during the 15-year follow-up period (p<0.001) (7.6 ± 0.82 and 8.17 ± 1.22, respectively) (Figure 2). In the subgroup analysis of CSII, SAP patients had lower mean HbA1c than standard CSII patients, 7.30 ± 0.73% and 7.84 ± 0.83%, respectively (p: 0.012). Total insulin dose and basal insulin ratio were similar between CSII and MDI groups until puberty. With the onset of puberty, basal insulin ratio and total insulin dose were significantly decreased in the CSII group (p: 0.029 and 0.018, respectively) (Table 2).

Number of hospitalizations [median 0.32 (0.06–3.63) times/year in CSII and 0.29 (0–1.19) in MDI group (p: 0.35)] and ketoacidosis attacks [median 0.04 (0–1.21) attacks/year in CSII and 0.07 (0–1.19) attacks/year in the MDI group (p: 0.41)] were not different between the two groups throughout the follow-up years.
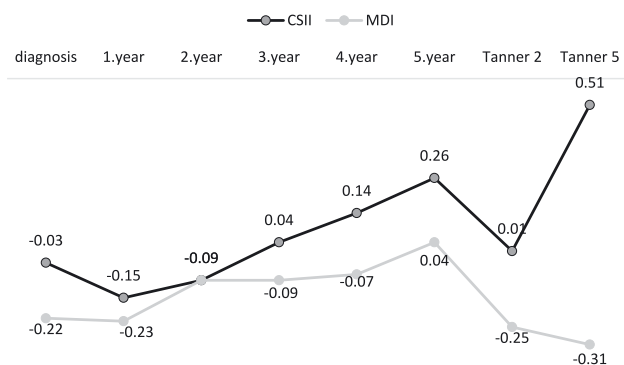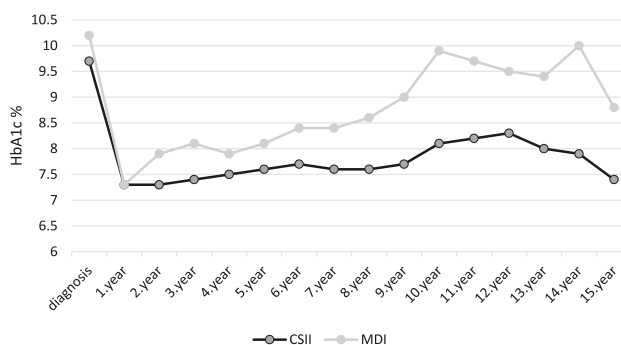

Figure 1: Height SDS of patients.

Figure 2: HbA1c variability during follow-up period.

Table 2: Total insulin dose, basal insulin ratio during follow-up period.

	Total insulin dose, U/kg/day					Basal insulin/total insulin ratio, %				
	CSII		MDI		p-Value	CSII		MDI		p-Value
	n	Mean ± SD	n	Mean ± SD		n	Mean ± SD	n	Mean ± SD	
Diagnosis	44	0.87 ± 0.57	26	0.82 ± 0.29	0.759	44	34.02 ± 14.04	26	36.22 ± 14.42	0.554
First year	50	0.81 ± 0.23	31	0.79 ± 0.21	0.679	50	38.92 ± 11.01	31	45.17 ± 15.05	0.055
Second year	49	0.81 ± 0.22	29	0.80 ± 0.22	0.826	49	41.99 ± 13.14	29	46.38 ± 15.12	0.237
Third year	44	0.80 ± 0.19	18	0.89 ± 0.25	0.118	44	43.50 ± 13.30	18	44.57 ± 16.90	0.793
Fourth year	39	0.84 ± 0.21	19	0.96 ± 0.28	0.063	39	40.30 ± 9.38	19	48.81 ± 16.24	**0.014**
Fifth year	33	0.81 ± 0.15	21	0.91 ± 0.28	0.125	33	40.90 ± 8.02	21	47.44 ± 16.15	0.096
Tanner 2	33	0.86 ± 0.19	14	1.02 ± 0.22	**0.029**	33	39.88 ± 8.30	14	47.91 ± 12.99	**0.018**
Tanner 5	21	0.94 ± 0.23	9	0.99 ± 0.28	0.656	21	45.35 ± 12.96	9	39.76 ± 13.52	0.348

CSII, continuous subcutaneous insulin infusion; MDI, multiple dose injection; SD, standard deviation. Bold values in the table are significant p values.

The incidence of complications was too low to draw any meaningful conclusions regarding the relative risk or benefits of either treatment. Three (6.5%) patients in the CSII group and four (9%) patients in the MDI group, totally seven (6.6%) patients developed persistent micro-albuminuria. Three (4.9%) patients in the CSII group and three (6.8%) patients in the MDI group, totally six (5.7%) patients developed neuropathy. Chronic autoimmune thyroiditis was detected in 15 (14.2%) patients, and celiac disease was detected in three (2.8%) patients.

Discussion

This study aimed to evaluate the difference of auxological findings and metabolic control in children with T1DM using either CSII or MDI. In the Prospective Diabetes Follow-up Registry (DPV) study, in children under 6 years of age, mean HbA1c was 7.4% using 74% CSII treatment [15]. Numerous observational studies with type 1 diabetes have reported decreases in HbA1c levels with CSII without increasing the risk of hypoglycemia [16, 17]. Our results supporting this demonstrate a better glycemic control in the CSII group (HbA1c: 7.62%) compared to the MDI group (HbA1c: 8.17%), below the average of our country [18, 19]. In the outcomes of the 2016–2018 T1D exchange registry report, CGM use increased in pediatric age groups; especially under 5 years of age (51%) and mean HbA1c was lowest in the SAP group. Under 13 years of age, mean HbA1c is 9.0% in MDI (n: 75) and 8.7% in standard pump group (n: 72) and 7.9% in SAP (n: 63) group [20]. Similarly in our study, the best HbA1c was achieved in patients using SAP therapy.

It is known that both boys and girls with T1DM are heavier and taller throughout childhood than healthy children. By contrast, in a study with 184 children with T1DM found that children aged 5–10 years at diagnosis were taller than controls at the same age, while those diagnosed at <5 years of age were shorter [21]. Alterations in growth have been reported in children with T1DM, although with discordant findings in different studies [22–26]. In the SCIPI RCT study, during one-year prospective follow-up, there was no significant difference in change of BMI or height SDS between CSII and MDI in pediatric patients, but as the 1-year follow up is not enough to conclude height [27]. For our cases, they were not taller or heavier than healthy peers at the time of diagnosis; mean weight SDS was: −0.24 ± 1.14 and height SDS was −0.16 ± 1.1, but after puberty height was higher in CSII patients than in MDI patients, although target height SDS of both groups was not different. MDI group height SDS was similar to their target height SDS. In our study, the final height could not be compared because very few patients were over 18 years old when the study was completed. Based on the information that, as puberty completed, a girl has reached 99% of her adult height at a bone age of 15 years and has a small amount of height growth left from this point, height SDS values were compared in children who completed puberty [28]. However, there is evidence of a secular trend in the heights of children over the last 20 years [29]. Considering this, the CSII group may demonstrate the expected growth, while the MDI group may not. This height difference may be due to a difference in metabolic control. Bonfig et al. collected the final adult height data of 1685 patients with T1DM who were diagnosed before the age of 10 years, notably, the group with HbA1c <7% had a final adult height SDS of +0.030, groups with HbA1c of 7–8% and >8% had final adult SDS values of −0.122 and −0.308, respectively; this suggested that poor glycemic control was associated with a slight reduction in final adult height [29]. Similarly, our MDI group patients' HbA1c was 8.17% and mean height SDS was −0.31. This also alone

cannot explain the +0.75 SDS increase from target adult height SDS in the CSII group, there should be a factor that influences pubertal growth spurt, as the height difference in our study groups occurs by then. This may be explained by studies of higher IGF-1 levels of good metabolic control than poor metabolic control patients [30]. They also have demonstrated high GH and low IGF-1 level in patients with T1DM in poor control like all chronic diseases affecting growth [21, 31], so IGF-1 levels were strongly correlated with height [24]. Because our study was retrospective, IGF-1 levels were not evaluated.

In our study group, CSII treatment was not started at the time of diagnosis in 53 patients (84%). This may seem like a limitation, but we think that it did not affect our results regarding height, since in all patients CSII therapy was applied before puberty and the mean follow-up period of patients who completed puberty was 11.8 ± 3.5 years.

In the DCCT study, short adult stature is associated with microvascular complications in type 1 diabetes and short stature was independently associated with both diabetic nephropathy and laser-treated retinopathy in addition to the conventional risk factors such as duration of diabetes, A1C, blood pressure [32]. These results suggest that diabetes influences height by different mechanisms in addition to IGF-1 and these mechanisms are also associated with microvascular complications. This can be studied by the effect of glycemic variability; at the same HbA1c values, patients may have different glycemic variabilities and increased variability can affect both complications and IGF-1/GH axis.

As known anabolic effects of insulin, and by using intensive insulin regimen, excessive weight gain and obesity are another common problem in children with T1DM. Increased BMI in youth with T1DM has been reported in clinic-based and national cohorts and is associated with a more atherogenic cardiovascular disease risk profile [33, 34]. In a retrospective study from Australia 20-year follow-up of 1975 children with type 1 diabetes, the proportion of overweight and obese children was higher than that in the general Australian pediatric population [35]. In a study, T1DM patients were found to be less active than their peers and this may contribute to adiposity [36]. In our study population, interestingly obesity ratio was lower than the general Turkish pediatric population (7.5–8.5%) [37].

As a controversial issue, CSII was associated with a significant increase in the incidence of reported DKA. Notably, the increased risk of DKA was significant in trials comparing CSII with conventional insulin therapy, whereas only a nonsignificant trend toward increased risk was observed in comparisons with basal-bolus MDI [38–40]. In our study, the DKA attack number or hospitalization number was not different between groups.

When the long-term effects of CSII treatment were investigated, it is hoped and estimated to reduce microvascular complication rates. Although studies have been shown that CSII treatment reduces arterial stiffness, decreases the frequency of retinopathy, reduces the progression of microalbuminuria, more studies are needed [41–43]. In our study, the number of complications was insufficient to make a statistical interpretation.

According to a SWEET prospective study, in 16570 children, daily insulin dose (U/kg/D) remained decreased when treated with CSII compared to MDI [44]. In our study subgroup analysis, also there is a tendency of low insulin dosage and basal ratio in the CSII group, only Tanner stage 2 was found to be statistically significant.

Conclusion

CSII treatment had positive effects on metabolic control and height SDS in patients with early-onset diabetes (under 5 years old) without increasing BMI and DKA. More studies are needed to find the causative agent of preventing pubertal spurt in diabetic patients, its relationship to glycemic variability may be a responsible factor.

Limitations

The current study was a retrospective study of one tertiary center patients in a developed city of Turkey; thus, cases of selection bias cannot be completely ruled out. Moreover, the small number of subgroups may not provide sufficient statistical power to fully elucidate the relationships between variables. Social security system payment is very little for pump therapy and additional reservoir and set fees are paid by families. Continuous glucose monitoring systems are out of insurance. Besides very few centers can't still apply CSII, this may lead to better socioeconomic status families that reached to us for CSII application. This may also be the cause of better metabolic control of our patients than Turkey's mean HbA1cs. We could not determine the glycemic variability and hypoglycemia because of the retrospective design of our study.

responsibility for the entire content of this submitted article and approved submission.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' Institutional Review Board (Ege University Ethics Comitee) or equivalent committee (approval number:20-1.1T/57).

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