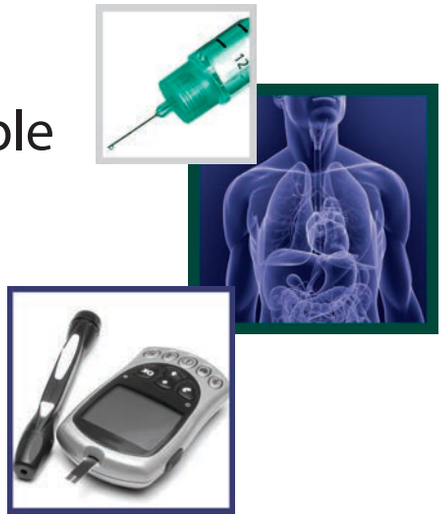
RESEARCH ARTICLE

Assessment of the impact of measurable behaviors on glycemic control using continuous subcutaneous insulin infusion



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Practice Points

- The success of glycemic control when using continuous subcutaneous insulin infusion (CSII) is known to be directly related to the number of daily boluses and blood glucose levels entered into the device.
- A glycemic target of ≤7.5% (58.5 mmol/mol) is sought for all youth with Type 1 diabetes mellitus at our center.
- This study aimed to explore the reasons why, despite apparently high levels of daily self-management, some youth with Type 1 diabetes mellitus do not attain or maintain this target using CSII.
- This retrospective study reviews the HbA1c and corresponding CSII behaviors as recorded from the downloaded information at both 3–6 and 12–18 months post-CSII commencement between April 2008 and 2010.
- Data were analyzed for 60 youth with a mean age of 11 ± 3.7 years.
- At 12–18 months post-CSII commencement, only 51.5% of youth had attained a HbA1c of ≤7.5% (58.5 mmol/mol).
- Measurable CSII behaviors alone do not predict glycemic trajectories, whereas glycemic control at baseline is an indicator of HbA1c at 12–18 months post-CSII commencement.
- Despite consistent adherence with clinical guidelines in terms of the numbers of daily boluses and blood glucose levels entered, a subgroup of patients fail to demonstrate the expected improvement in glycemic control in the medium term.
- In the future, we plan to explore the potential barriers to glycemic improvement, which include a possible clinical manifestation of the fear of hypoglycemia or a 'passive' attitude towards diabetes management.

SUMMARY **Aim:** To explore continuous subcutaneous insulin infusion (CSII) behaviors in a pediatric population with Type 1 diabetes mellitus, and their association with glycemic control. **Research design & methods:** Youth were defined as 'within target' (HbA1c

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≤7.5%/58.5 mmol/mol) and 'above target' (HbA1c >7.5%/58.5 mmol/mol), 12–18 months post-CSII. The above-target group was subdivided into: 'adherent yet above target' (at least four blood glucose levels and at least six bolus wizard events entered per day) and 'nonadherent' (fewer than four blood glucose levels or fewer than six bolus wizard events entered per day). **Results:** Out of 60 patients, 51.5% (31 out of 60) were within target. Adherent yet above target youth demonstrated similar CSII behaviors to the within-target group, yet their glycemic trajectory mimicked that of their nonadherent peers. **Conclusion:** CSII requires users to be target driven and proactive in adjusting settings to achieve glycemic control. A 'passive' attitude towards CSII is potentially as detrimental to glycemic control as frank nonadherence to recommended behaviors.

Glycemic control with continuous subcutaneous insulin infusion (CSII) use is related to the number of blood glucose level (BGL) and daily bolus events (combining food and correction boluses) entered into the device [1–4]. Our center, therefore, recommends that a minimum of four BGL and six bolus wizard events (BWEs; comprising both food and correction boluses) are entered into the pump daily, using the bolus wizard function. Failure to incorporate these recommendations is known to result in suboptimal glycemic control [3]. These important associations are routinely reinforced at our standardized CSII initiation and routine follow-up clinic sessions, which are scheduled every 3–4 months as standard for all patients regardless of insulin delivery modality. Education is provided regarding basal rates and CSII ratios (carbohydrate and insulin sensitivity factor) and the impact that these factors have on blood sugar levels; however, many youth still struggle to attain the target HbA1c of ≤7.5% (58.5 mmol/mol) despite apparently high levels of self-management. This study aimed to explore the prevalence of, and further characterize, the subset of patients who demonstrate high levels of user–pump interaction and yet fail to achieve HbA1c targets.

Research design & methods

This was a retrospective all-of-clinic study of patients with Type 1 diabetes mellitus (T1DM) commenced on Medtronic (MC, USA) insulin pump devices. All patients with download data (Medtronic Carelink™) at both 3–6 and 12–18 months after CSII initiation were included, when an initial improvement in glycemic control is expected with a subsequent deterioration towards baseline; patients were excluded if the available CSII data were obtained outside of these timepoints. HbA1c (HPLC ion exchange, Bio-Rad D10™; Bio-Rad, CA, USA) levels were documented at CSII initiation and at the time of data downloads. Baseline characteristics, including age and duration of T1DM at CSII initiation, as well as BMI z-scores and pre-CSII insulin regimens, were documented. Total daily doses of insulin were documented prior to CSII and at the time of the 3–6 and 12–18 month downloads. In the absence of the measurement of C-peptide levels, an assessment of the possibility of a partial remission ('honeymoon phase') was made using the insulin dose-adjusted HbA1c (IDAAC; calculated by HbA1c [%] + [4 × insulin dose per kilogram per day]) prior to CSII commencement, whereby a calculated value of ≤9 indicated a partial remission [5]. CSII-related behaviors recorded included mean frequency of BGLs and number and types of BWE entered daily, frequency of line changes, CSII suspension times and mean BGL values obtained from the Carelink download information. The indication for CSII referral was identified from clinical records where available. Subjects were classified according to glycemic control at 12–18 months post-CSII commencement, and were defined as 'within target' (HbA1c ≤7.5%/58.8 mmol/mol) or 'above target' (HbA1c >7.5%/58.5 mmol/mol). The above target group was then further subdivided according to their level of user–pump interaction to encompass: 'adherent yet above target' (HbA1c >7.5%/58.5 mmol/mol, with at least four BGLs and at least six BWEs entered per day) and 'nonadherent' (HbA1c >7.5%/58.5 mmol/mol, with fewer than four BGLs or fewer than six BWEs entered per day) subgroups. Comparisons were made using the student t-test, where $p \leq 0.05$ was considered significant.

Results

At the time of publication, over 1600 children and young adults were attending The Royal Children's Hospital (Melbourne, Australia) for management of T1DM, 580 of whom are currently using CSII. Data were analyzed for 60 youth (31 male), aged 11.0 ± 3.7 years (range: 3.4–18.2 years), who commenced CSII between April 2008

and 2010. During this time period, a total of 117 youth were initiated on CSII, of whom 92 were using a Medtronic device. Youth were only excluded if the required data were not available. Overall, HbA1c was 8.0% (63.9 mmol/mol) pre-CSII, 7.4% (57.4 mmol/mol) at 3–6 months and 7.5% (58.5 mmol/mol) at 12–18 months ($p < 0.01$). While 50 out of 60 (83.3%) of the cohort met our BGL and BWE recommendations at 12–18 months, only 31 out of 60 (51.7%) were within target. A total of 19 (65.5%) youth were adherent yet above target, while the remaining ten out of 29 (34.5%) were nonadherent to recommended CSII behaviors. The nonadherent group were older at CSII initiation with a longer duration of diabetes when compared with the within-target group alone ($p < 0.01$), as shown in Table 1 along with patient characteristics and insulin regimens prior to CSII commencement. Only one patient, a female in the within-target group, had an IDAAC value of ≤9 at baseline, and continued to do so for the duration of the study period.

BMI prior to CSII commencement was within the normal range for all three groups, with some statistical differences between the groups in the absence of clinical significance (within target vs adherent yet above target: $p = 0.7$; within target vs nonadherent: $p = 0.03$; and adherent yet above target vs nonadherent: $p = 0.004$). Baseline total daily doses of insulin on pre-CSII regimens were similar in the within-target and adherent yet above target groups ($p = 0.6$), but increased in the older nonadherent group ($p = 0.02$ and 0.07, respectively). When pre-CSII insulin requirements were compared with those at follow-up, all groups showed a decrease in total daily doses per kilogram at both 3–6 and 12–18 months ($p \leq 0.02$ in each case).

Comparison of CSII behaviors showed equivalent levels of daily BGL and BWE in the within-target and adherent yet above target groups, consistent over time (Figure 1A & 1B). By contrast, the nonadherent group initially demonstrated recommended levels of CSII behaviors at 3–6 months, which were not sustained at 12–18 months.

Mean HbA1c at CSII-initiation for the within-target group was 7.6% (59.6 mmol/mol), 7.0% (53.0 mmol/mol) at 3–6 months ($p < 0.001$) and 6.9% (51.9 mmol/mol) at 12–18 months ($p < 0.0001$) (Figure 1C). By contrast, despite disparate user–pump interaction levels, glycemic trajectories of adherent yet above target and nonadherent groups were similar. Although some initial improvement in glycemic control was seen in these subgroups, by 12–18 months mean HbA1c had returned to pre-CSII suboptimal levels.

Mean BGL values were consistently lower in the within-target versus adherent yet above target groups at 3–6 and 12–18 months (Table 1). These groups had similar percentages of time spent below CSII target BGL (3–6 months: $p = 0.5$; 12–18 months: $p = 0.18$), but differed significantly in the percentage of time spent above this value (3–6 months: $p = 0.019$; 12–18 months: $p = 0.019$). Neither bolus type nor total daily doses of insulin differed between the groups. No differences were seen in the frequency of CSII line site changes or CSII suspension times (data not shown).

Table 1. Patient characteristics and continuous subcutaneous insulin infusion-related information.

Characteristics	Within target	Adherent yet above target	Nonadherent
Patient characteristics at CSII start			
Male (n)	31 (16)	19 (8)	10 (7)
Age (years)	10.7 ± 3.4	10.0 ± 3.4	14.2 ± 1.8*
Duration of T1DM (years)	2.7 ± 1.8	3.8 ± 2.7	5.7 ± 4.2*
BMI z-score	0.5 ± 1.0	0.6 ± 0.9	0.6 ± 0.7
Total daily insulin dose (U/kg per day)	1.0 ± 0.4	1.0 ± 0.4	1.3 ± 0.4**
IDACC†	11.5 ± 2.0	12.5 ± 1.6	13.6 ± 2.1
Insulin regimens			
▪ BD	23 (74.2)	14 (73.7)	6 (60)
▪ MDI	8 (25.8)	5 (26.3)	4 (40)
BGL (mmol/l)			
3–6 months	8.8 ± 1.4	9.7 ± 2.0**	10.5 ± 1.7**
12–18 months	8.9 ± 1.4	9.9 ± 1.6**	10.0 ± 2.2**
Time above target (%)			
3–6 months	47.4 ± 13.4	57.2 ± 14.7**	63.2 ± 11.8**
12–18 months	48.4 ± 14.1	58.3 ± 14.0**	58.5 ± 23.7**
Time below target (%)			
3–6 months	10.5 ± 5.2	9.3 ± 6.6	5.7 ± 8.6
12–18 months	11.6 ± 7.6	8.8 ± 6.4	5.4 ± 3.4
Total daily insulin dose (U/kg per day)			
3–6 months	0.74 ± 0.2	0.76 ± 0.16	0.9 ± 0.22
12–18 months	0.8 ± 0.27	081 ± 0.14	0.89 ± 0.19
Basal insulin (% of total daily dose)			
3–6 months	41.4 ± 5.6	43.9 ± 4.8	43.9 ± 7.0
12–18 months	40.6 ± 7.5	42.8 ± 5.7	47.6 ± 6.6

Results are presented as mean ± standard deviation, with the exception of insulin regimens, which are shown as number of patients (%). Time above and below target refers to the number of BGL readings (%) entered into the pump, which are <4 mmol/l or >7.8 mmol/l as directed by CSII settings. Significant comparisons between the 'within target' and 'adherent yet above target' or 'nonadherent' groups are shown.
†IDACC calculated as HbA1c (%) + (4 × insulin dose/kg per day), whereby a value ≤9 indicates partial remission ('honeymoon phase').
*$p \leq 0.01$; **$p \leq 0.05$.
BD: Twice daily; BGL: Blood glucose level; CSII: Continuous subcutaneous insulin infusion; IDACC: Insulin dose-adjusted HbA1c; MDI: Multiple daily insulin; T1DM: Type 1 diabetes mellitus.

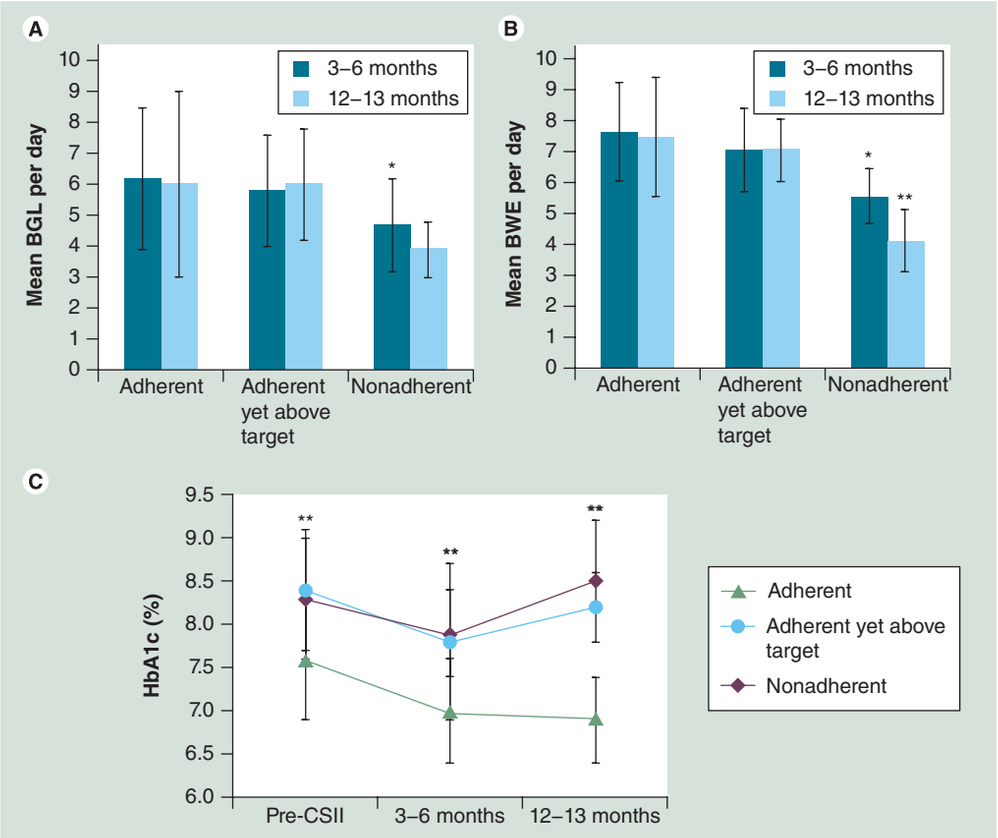

Figure 1. Summary of daily continuous subcutaneous insulin infusion tasks and HbA1c trajectories. Comparision of **(A)** daily BGLs, **(B)** BWEs and **(C)** HbA1c trajectory. Results are presented as mean ± standard deviation. P-values are shown for comparison between the 'within-target', 'adherent yet above target' and 'nonadherent' groups. Other comparisons were nonsignificant ($p > 0.05$). HbA1c is shown in the National Glycohemoglobin Standardization Program (NGSP) units (%), whereby the International Federation of Clinical Chemistry (IFCC) unit (mmol/mol) is derived from the following formula: 10.93 × HbA1c% – 23.5.
*$p < 0.05$; **$p < 0.001$.
BGL: Blood glucose level; BWE: Bolus wizard event; CSII: Continuous subcutaneous insulin infusion.

A formal record of indication for CSII referral was available in only 37 out of 61 patients (51.7%); of these, 'recurrent hypoglycemia' prompted referral in only two patients, both with mild recurrent hypoglycemia and both in the within-target group. For the remainder, 'lifestyle', 'improved control' or a combination of the two were cited.

Conclusion

The overall glycemic trajectory of this cohort reflects both our institutional CSII experience and that of other centers [6,7]; however, the fact that 48.3% fail to achieve our universal target HbA1c ≤7.5% (58.5 mmol/mol) 12–18 months post-CSII initiation indicates deficits in daily management. This is a particular concern for the 19 out of 60 patients (31.6%) for whom this is true despite their adherence to measurable daily management tasks that are prescribed based on published associations with glycemic outcomes. While older age at CSII start and frank nonadherence with recommended levels of user–pump interaction were, again, associated with HbA1c >7.5% (58.5 mmol/mol), these current data demonstrate that measurable CSII behaviors alone do not predict glycemic outcomes in all patients. Glycemic control at baseline predicts follow-up HbA1c at 12–18 months post-CSII initiation and may serve as a guide for CSII suitability [1,8,9]. Exploration into the potential reasons for this is beyond the scope of this paper, but it

is likely to be multifactorial, including pre-CSII adherence to clinical recommendations, belief systems and behavioral patterns.

Notably, no change in CSII behaviors occurred in the adherent yet above target group to explain the deterioration in HbA1c at 12–18 months. This group exhibited consistently high levels of daily CSII behaviors, almost identical to those of the within-target group. By contrast, they not only failed to obtain glycemic benefits, but their HbA1c trajectory mimicked the poor outcomes seen in 'nonadherent' youth, suggesting that perhaps the quality of these behaviors is somehow different between the groups.

There are a number of possible explanations for this discrepancy between pump interaction and glycemic outcomes. All patients demonstrated a reduction in daily insulin doses, which appears to be inappropriate in the context of the increasing HbA1c of the adherent yet above target and nonadherent groups [10]. Based on the calculated IDAAC values, a partial remission phase does not appear to be contributory [5]. The onset of adolescence, with its associated insulin resistance, may have an effect in addition to nonadherence with clinical recommendations and diminishing parental involvement in diabetes management, which may explain the suboptimal and deteriorating control of the older nonadherent group. However, it does not account for the diverging glycemic trajectory of the within-target and adherent yet above target groups. Both of these groups share similar baseline characteristics, including age, BMI and insulin doses, and they also demonstrate equivalent levels of CSII-related interaction; yet the latter have higher mean BGL levels and spend a greater percentage of time above the CSII programmed target BGL. Despite standardized education emphasizing the importance of ensuring that correction boluses attain BGLs close to target (5.0 ± 0.5 mmol/l), this group appeared to accept hyperglycemia. It is possible that the adherent yet above target group have made an active decision to avoid hypoglycemia, and as a consequence allow higher mean BGLs as a protective measure. However, from the limited information on indications for CSII in this cohort, it appears that significant hypoglycemia preceding CSII is not contributory. It is also possible that a 'passive' attitude, characterized by a lack of reflective practice or target-driven care may be causative.

The value of the findings of this study is limited by its retrospective nature and small sample size; a meaningful assessment in terms of gender, pubertal status, frequency of allied health contact, the number of changes to pump settings over the study period, frequency of blood glucose testing not entered into the CSII device, history of severe hypoglycemia/diabetic ketoacidosis and reasons for CSII referral could not be accurately assessed. A prospective study would be useful to address not only these issues, but also to examine patterns in the timing of boluses, glucose variability and postprandial hyperglycemia indicative of insulin resistance [11]. The cohort was limited to those who were commenced on a Medtronic CSII device due to the availability and clinical use of the companion Carelink software. A questionnaire tool or psychological assessment would be required to formally address patient/parent attitudes to CSII and glycemic control in order to define whether or not a passive attitude is truly accountable for the glycemic trajectory of the adherent yet above target group, or if it represents a significant fear of hypoglycemia.

CSII is an intensive insulin regimen that offers patients with T1DM flexibility in terms of lifestyle. For success in terms of attainment of the glycemic targets that are essential for long-term health benefits, adherence to clinical guidelines is essential and is more likely to be achieved by those with a HbA1c that is approximately 7.5% (58.5 mmol/mol) at baseline. This should be emphasized to patients/parents during pre-CSII counseling, as target setting is known to correlate with glycemic control [12]. Regardless of the possible physiological or psychological antecedents, it is concerning that only 51.6% of this cohort achieved their target HbA1c. Given that pediatric patients with T1DM are routinely reviewed in the clinic setting on a 3–4-monthly basis, it is vital that active self-management occurs in the intervening periods. We propose that our data may indicate that a passive attitude to CSII in the adherent yet above target group, whereby patients and families (or their healthcare professionals) do not proactively intervene to alter CSII settings to reduce hyperglycemia, may be as detrimental to the achievement of HbA1c targets as frank nonadherence. The fact that 31.6% of our cohort was adherent yet above target indicates that the negative impact of 'passive pumping' may be a common clinical entity, and successful progression into a more active model of self-management has the potential to significantly improve the glycemic benefits attained. Interventions to empower CSII users to confidently attain target

BGLs are currently being introduced and will be prospectively monitored.

Future perspective

The use of CSII has become an accessible and feasible treatment option in the management of children with T1DM. With increasing demands on limited resources, there is a corresponding increase in pressure on clinicians to deliver cost-effective and efficacious healthcare. The results of this study have shown that CSII use is not successful in terms of glycemic control for all patients at our center, which confirms our anecdotal experience. Previously, formal education was given at CSII commencement and was clinician-, patient- and parent-dependent thereafter. We plan to introduce an intervention program that will be offered to all CSII users at our center, aiming to explore the potential barriers to optimal glycemic control and provide the practical skills and motivation to achieve and maintain HbA1c within the target of ≤7.5% (58.5 mmol/mol).

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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