conventional regimen may be a result of optimal use of this regimen in specific centers.(26) At our center, families using 'conventional' insulin therapy do receive multidisciplinary diabetes education, use carbohydrate counting daily as they typically plan for a pre-determined amount of carbohydrates with each meal, and adjust doses of their rapid insulin analogue at breakfast and dinner based upon blood glucose levels. These site-specific factors may decrease the likelihood that the change in HbA_{1c} seen with IPT in our study represents factors associated with intensification or education rather than change to IPT. Indeed, prior regimen was not significant in univariate analysis, and a sensitivity analysis further adjusting for prior regimen showed almost identical results to the presented regression model. Nonetheless, it must be considered that 'intensification' for some or all families as they moved from injection to pump therapy could have played a role in the improvement seen with IPT. The specific characteristics of our study population must be kept in mind when considering the change in glycemic control that occurred with IPT.

The low percentage of youth on a multiple daily injection basal-bolus insulin regimen prior to IPT in our study highlights a significant limitation in insulin therapy options that face youth living in regions where schools are not able to support intensive insulin injection regimens. In such situations, IPT may well be the only feasible option for a child to receive intensive diabetes management in the school setting. Our study demonstrates that for youth for whom local factors dictate they are on a conventional insulin injection routine, such as in British Columbia under the timeframe of this study, transition to IPT can lead to improved HbA_{1c}.

Our analysis identified other factors associated with the change in HbA_{1c} after pump start. A higher age at pump initiation, BMI Z-score and a delay in pump initiation since diabetes diagnosis were associated with an increase in mean post-pump HbA_{1c}, compared to pre-pump mean HbA_{1c}, while male gender was associated with decrease in mean post-pump HbA_{1c}, compared to pre-pump mean HbA_{1c}. However, these

were not our primary hypotheses, so these findings should be interpreted with caution. Further studies are required to confirm these findings.

With regards to all study participants, we observed an overall decrease in HbA_{1c} over the 18-month follow-up period after pump initiation of 0.48% [5.2 mmol/mol]. This is consistent with two meta-analyses in adult and pediatric populations,(29,30) as well as several studies in children,(31,32) which demonstrated improved glycemic control with IPT. Of note, it has been shown in several pediatric studies that HbA_{1c} may decrease initially following pump initiation, and then gradually increase closer to baseline when followed long-term; however, still maintaining HbA_{1c} levels below the pre-pump values.(18,20,33,34) One possibility for this observed effect is the increased contact and follow-up by diabetes educators in the initial time after IPT initiation, as well as increased adherence while adjusting to a new routine.

Strengths of this study are that it represents all insulin pump starts at a tertiary Canadian hospital over a five-year period. Furthermore, the analysis of change in HbA_{1c} was rigorous in that it excluded honeymoon period HbA_{1c} values, and used robust statistical analysis to account for longitudinal and correlated data along with adjusting for the confounding variables.

Limitations of this study include the retrospective data collection, relatively small group size when stratified into levels of pre-pump HbA_{1c}, and the relatively short follow-up period of 18 months. Additionally, as this study was not randomized, there may be unmeasured confounding. Being a single-site study may limit the generalizability of the results to other heterogeneous populations, as the population of this study reflects the current state of diabetes care in British Columbia during this timeframe. Firstly, while there was universal coverage for insulin pumps, there was no universal or private coverage for CGM. This coupled with the small number of participants in the individual pre-pump metabolic control groups restricted our ability to adjust for CGM. However, the result from the

regression analysis on the full cohort with and without CGM was very similar reinforcing our confidence in the results. Secondly, there was initially no, and subsequently limited, ability for insulin administration at school, leading most children to be on conventional insulin routines prior to IPT. Even though our analysis adjusted for a range of potential confounding variables, socioeconomic status is as an important co-variant which the present data set is unable to address. Additionally, we did not have information on parental education and supplemental insurance coverage. Finally, this study excluded children who did not have sufficient pre-pump HbA_{1c} data available for analysis.

Our study demonstrates for the first time in a large cohort of young children the varying degree of *improvement* in HbA_{1c} after IPT initiation based on the children's pre-pump HbA_{1c} after controlling for other potentially confounding variables. Children who had poor metabolic control prior to IPT initiation showed the greatest improvement, followed by those with moderate and good pre-pump metabolic control. These results highlight that eligibility and consideration for IPT should be expanded to routinely include children with high HbA_{1c}.

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All authors were involved in study design and analysis plan, contributed to the data interpretation, and edited the manuscript. SB collected data and prepared the first draft of the manuscript. NI conducted the data analysis. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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TABLES

TABLE 1: Baseline characteristics of patients included in the analysis of effects of insulin pump therapy on HbA_{1c}, divided into pre-pump metabolic control groups

	Pre-pump metabolic control*			
Factor	Good (N=37)	Moderate (N=72)	Poor (N=16)	Overall (N=125)
Age at Diagnosis; median (IQR)	9 (6.7, 11.5)	6.1 (2.8, 10.1)	2.6 (1.7, 8.8)	7.4 (2.7, 10.1)
Gender; n (%)				
Male	20 (54)	36 (50)	5 (31)	61 (49)
Female	17 (46)	36 (50)	11 (69)	64 (51)
Continuous glucose monitoring; n (%)				
No	36 (97)	69 (96)	16 (100)	121 (97)
Yes	1 (3)	3 (4)	-	4 (3)
Age at pump initiation (years); median (IQR)	11.1 (9, 14.1)	10.3 (6.1, 14.4)	11.9 (5.6, 15.8)	11 (6.9, 14.4)
Time from diagnosis to pump initiation (months); median (IQR)	22.7 (13.5, 39.2)	31.6 (16.6, 58.4)	58 (24.5, 106.5)	29 (16.7, 57.3)
Height z-score; median (IQR)	0.3 (-0.5, 1.4)	0.2 (-0.6, 1.1)	0.1 (-0.3, 0.6)	0.2 (-0.5, 1)
Weight z-score; median (IQR)	0.4 (0.1, 1.4)	0.9 (0.2, 1.4)	0.7 (0.1, 1.4)	0.7 (0.1, 1.4)
BMI z-score; median (IQR)	0.4 (-0.2, 1.3)	0.9 (0.4, 1.5)	0.7 (0.5, 1.5)	0.7 (0.3, 1.4)
Insulin regimen prior to pump therapy; n (%)				
Multiple daily injections	7 (19)	14 (19)	3 (19)	24 (19)
Conventional	30 (81)	58 (81)	13 (81)	101 (81)
Pump Brand; n (%)				
1	8 (22)	13 (18)	1 (6)	22 (18)
2	16 (43)	29 (41)	6 (38)	51 (41)
3	13 (35)	29 (41)	9 (56)	51 (41)

*Mean HbA_{1c}: Good: <7.5% [<58 mmol/mol]; Moderate: 7.5-9.0% [58-75 mmol/mol]; Poor: >9.0% [>75 mmol/mol]

IQR: Interquartile range. BMI: Body mass index

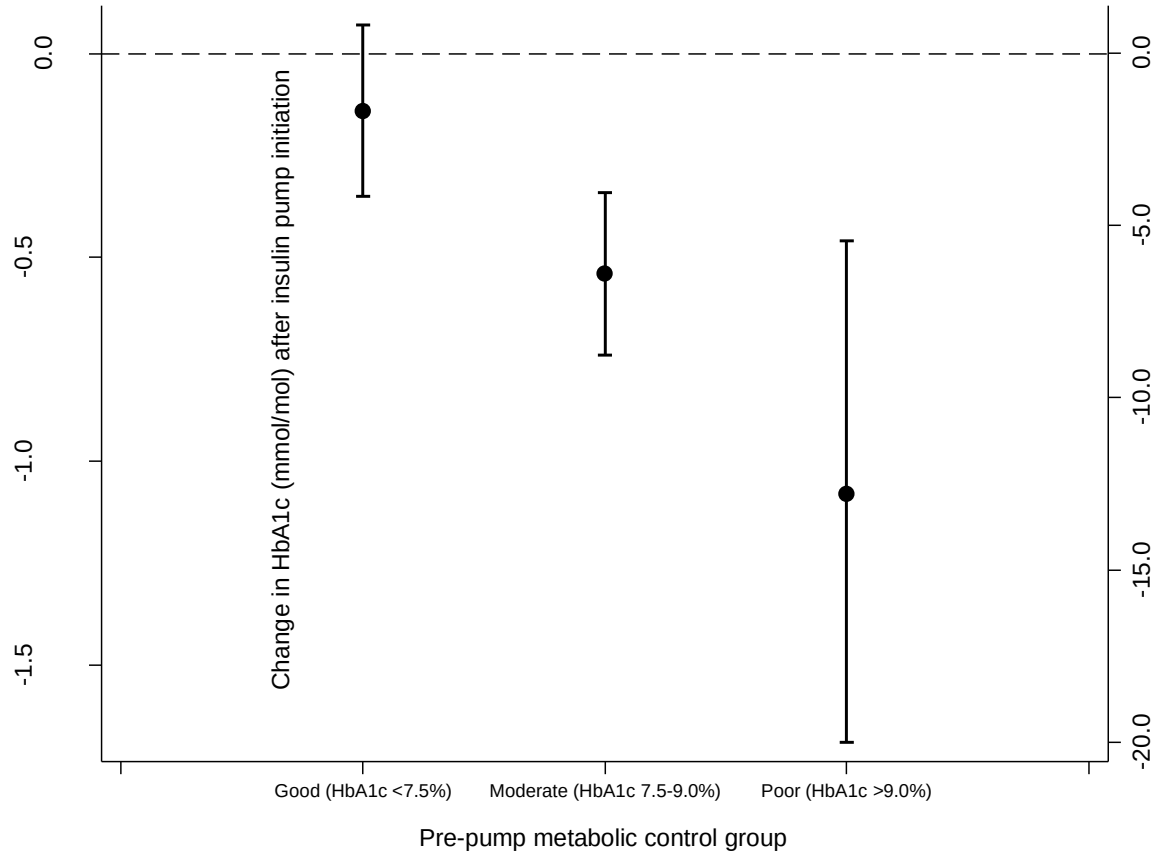
Table 2: Unadjusted and adjusted analysis from generalized estimating equation showing changes in mean HbA_{1c} (%) before and after pump initiation

Characteristics	Unadjusted mean change in HbA_{1c} (%)	p-value	Adjusted mean change in HbA_{1c} (%)	p-value
Age at pump initiation	0.02 (-0.01, 0.05)	0.222	0.03 (0.01, 0.05)	0.002
Gender				
Male	-0.32 (-0.6, -0.04)	0.025	-0.16 (-0.31, -0.02)	0.028
Female	*Ref*		*Ref*	
Each year since diabetes diagnosis to pump initiation	-0.03 (-0.15, 0.09)	0.6	0.25 (0.10, 0.40)	0.001
Body mass index Z-score	0.19 (0.04, 0.34)	0.014	0.10 (0.03, 0.18)	0.007
Insulin regimen prior to pump therapy				
Multiple daily injections	-0.04 (-0.39, 0.3)	0.802		
Conventional	*Ref*			
Pump Brand				
1	-0.43 (-0.76, -0.1)	0.011	-0.12 (-0.30, -0.06)	0.192
2	-0.02 (-0.35, 0.3)	0.885	-0.21 (-0.38, -0.03)	0.021
3	*Ref*		*Ref*	
Continuous glucose monitoring				
No	*Ref*		*Ref*	
Yes	-0.75 (-1.40, -0.10)	0.024	0.04 (-0.53, 0.61)	0.893
Insulin Pump				
Pre-pump	*Ref*		*Ref*	
Post-pump	0.08 (-0.07, 0.23)	0.303	-0.48 (-0.64, -0.33)	<0.0001

Adjusted model was additionally adjusted for baseline HbA_{1c} to address the issue of regression towards the mean

FIGURES

Figure 1: Adjusted changes in mean HbA_{1c} before and after insulin pump initiation (stratified by pre-pump metabolic control groups) from generalized estimating equations



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