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Research Article

ADHERENCE TO INSULIN IN SINGAPOREAN PEDIATRIC TYPE 1 DIABETES PATIENTS AND ITS IMPACT ON GLYCEMIC CONTROL AND HEALTH-CARE UTILIZATION

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ABSTRACT

Objective: Optimizing glycemic control is challenging with insulin non-adherence. This study aimed to characterize the prevalence of non-adherence among Singaporean pediatric patients with type 1 diabetes mellitus (T1DM) and investigate its associated outcomes.

Methods: Singaporean patients with T1DM aged ≤18 years old with ≥1 year of insulin prescription between 2012 and 2016 were included in this retrospective, single-center longitudinal study. Patients on insulin pumps were excluded from the study. Non-adherence was defined as medication possession ratio (MPR) <100%. Glycemic control was defined using mean hemoglobin A1c (HbA1c) within the study period. Health-care utilization was defined as the number of outpatients, inpatient, and emergency visits. The t-test, Chi-square test, logistic regression, and Poisson regression were used to analyze means, proportions, factors associated with non-adherence, and association of non-adherence and health-care utilization, respectively. Sensitivity analyses were performed for MPR thresholds of 80% and 95%.

Results: A total of 206 patients were included in this study. Non-adherent patients were older, had a longer duration of diabetes since diagnosis and shorter duration of follow-up. Gender, race, financial class, and number of concurrent medications were comparable between groups. The prevalence of non-adherence was 34.0% (95% confidence interval [CI]: 27.9–40.7%). Non-adherent patients had a higher average HbA1c (non-adherent: 9.6% [2.1] vs. adherent: 8.6% [1.3], p<0.001). Non-adherence was not associated with health-care utilization. Patients with >5 years of diabetes were more likely to be non-adherent.

Conclusion: Non-adherence defined as MPR <100% is associated with poorer glycemic control. Further interventions may focus on patients with >5 years of diabetes to improve their adherence to insulin therapy.

Keywords: Adherence, Insulin, Pediatrics, Type 1 diabetes, Health-care utilization, Glycemic control, Medication possession ratio.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) affects over one million children and adolescents worldwide [1] and is associated with significant morbidity and mortality [2]. It is a chronic condition characterized by the autoimmune destruction of pancreatic β-cells, leading to partial, or in most cases, and absolute insulin deficiency. Hence, exogenous insulin therapy, either in the form of multiple daily injections or an insulin pump, has become vital in the management of T1DM to optimize glycemic control.

Non-adherence is common among pediatric patients with T1DM, with 16–49% being non-adherent to insulin therapy [3]. Consequently, achieving optimal glycemic control continues to be a challenge for these patients. Poor glycemic control confers a risk of microvascular complications such as retinopathy, nephropathy, and neuropathy as well as macrovascular complications such as cardiovascular disease, heart attack, and stroke. However, these complications can be minimized if glycemic control is achieved early in the course of the disease as demonstrated by the Epidemiology of Diabetes Interventions and Complications study [4]. Moreover, sustained glycemic control may provide potential benefits such as improving patients' quality of life and greater cost savings for the health system [5].

Various measures of non-adherence exist for patients with diabetes, namely, patient self-reports, clinician reports, and pharmacy refill data [6]. The medication possession ratio (MPR), derived from pharmacy refill data, is the most common measure of non-adherence [7]. While the prevalence of insulin non-adherence among Singaporean type 2 diabetes has been characterized previously [8], it may not be reflective of pediatric patients with T1DM due to lifestyle, developmental and psychosocial differences, and an additional dimension of caregiver involvement among pediatric patients [9]. Hence, this study aimed to investigate the prevalence of insulin non-adherence among Singaporean pediatric patients with T1DM and the impact of non-adherence on glycemic control and health-care utilization. The factors associated with non-adherence were also examined to help tailor programs suited for these patient groups in an effort to improve health outcomes.

METHODS

Study design

This was a retrospective, single-center longitudinal study of patients with T1DM in the largest pediatric hospital in Singapore. Electronic medical and pharmacy refill records for insulin were screened for inclusion. Singaporean patients with T1DM aged 18 years and below who had at least 1 year of continuous prescription of insulin between January 2012 and December 2016 were included in the study. Patients on insulin pumps or those who were followed-up in other institutions were excluded from the study.

The study is approved by the SingHealth Centralized Institutional Review Board and conforms to the provision of the Declaration of Helsinki.

Outcome measures

The primary outcome measure was adherence, which is generally defined as the extent to which patients consume their medication as prescribed by their health-care providers [9]. Adherence was measured using the MPR, which was calculated by dividing the days of medication collected by the days of medication prescribed within the follow-up period [10]. Pharmacy refill records were obtained from the pharmacy dispensing system (MaxCare; iSOFT, Adelaide, South Australia). The number of days of insulin supplied for each visit was estimated based on the doses of insulin prescribed, taking into account the expiry date of the insulin vial or pen once opened.

As T1DM is a condition where there is a complete or almost complete lack of endogenous insulin production, absolute adherence to insulin therapy is important to avoid potentially life-threatening situations such as diabetic ketoacidosis. Hence, non-adherence to insulin was defined as having a MPR of <100% in this study. As rapid-acting insulin and long-acting basal insulin injections are both important in the basal-bolus insulin, patients were considered non-adherent as long as the MPR for one type of insulin was <100%.

The secondary outcomes include the impact of non-adherence on glycemic control and health-care utilization. Glycemic control was measured using the average hemoglobin A1c (HbA1c) within the follow-up period. Health-care utilization was measured using the number of outpatient visits, inpatient admissions, and emergency visits. Outpatient visits were further classified into endocrine, diabetes-related (endocrine, dietician, ophthalmic, and psychiatry) as well as all-cause visits. Inpatient admissions and emergency visits were also categorized into diabetes-related and all-cause admissions or visits. In addition, factors associated with non-adherence were explored. The relevant patient demographics were extracted from the institution's computerized physician order entry system (Sunrise Clinical Manager; Eclipsys, Atlanta, Georgia).

Data analysis

The prevalence of non-adherence estimated with pharmacy refill records ranged between 28.1% and 31.6% among pediatric patients with T1DM [11,12]. Assuming a non-adherence level of 30% and precision of 10%, a sample size of 81 would be required. A precision of 10% was used as this was a preliminary study exploring the prevalence of non-adherence among pediatric patients with T1DM in Singapore [13]. Patients' demographics and baseline characteristics were summarized using descriptive statistics. Continuous variables were analyzed using the independent sample t-test, while categorical variables were compared using the Chi-square test, or Fisher's exact test where appropriate. Poisson regression was used to analyze the relationship of count data such as outpatient, inpatient, and emergency visits with non-adherence, while adjusting for age, gender, race, financial class, presence of comorbidities, number of daily injections, average HbA1c, and duration of diabetes since diagnosis. To identify possible factors affecting adherence, logistic regression analysis was performed with adherence as the dependent variable and baseline characteristics as the independent variable. Sensitivity analyses were also conducted for the MPR threshold of 95% and 80%. Data were analyzed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA).

RESULTS

The flow diagram for patient selection is presented in Fig. 1. Out of 503 eligible patients identified, 206 patients were included in the analysis. The analysis sample had an equal proportion of males and females, with 68.4% Chinese, 16.0% Malay, 12.6% Indians, and 2.9% of other ethnicities. The majority of the patients in the study cohort (57.3%) were in puberty while a small proportion (3.4%) of the patients had hypothyroidism. No patient in the study cohort had concurrent celiac disease. A total of 70 patients were classified as non-adherent to insulin. Patients in the non-adherent group were older than patients in the adherent group (mean [SD] 12.4 years [4.1] vs. 11.6 years [3.7], respectively, p=0.001), and had a longer duration of diabetes since diagnosis (mean [SD] 4.7 years [4.3] vs. 2.6 years [3.3], respectively, p=0.001). In addition, patients in the non-adherent group had a shorter follow-up period compared with patients in the adherent group (mean [SD] 3.2 years [1.2] vs. 3.6 years [1.2], respectively, p=0.035). All other patient characteristics including gender, race, height, weight, body mass index (BMI) category, pubertal status, presence of comorbidities, financial status, proportion of patients engaged with exercise and self-monitoring of blood glucose, number of concurrent medications, and number of injections required daily were comparable between both groups. The baseline characteristics of the study cohort are summarized in Table 1.

Prevalence of non-adherence

The prevalence of non-adherence was estimated to be 34.0% (95% confidence interval [CI]: 27.9–40.7%). At a MPR threshold of 95% and 80%, the prevalence of non-adherence was estimated at 25.2% (95% CI: 19.8–31.6%) and 11.2% (95% CI: 7.6–16.2%), respectively. Details of the sensitivity analyses are summarized in Table 2.

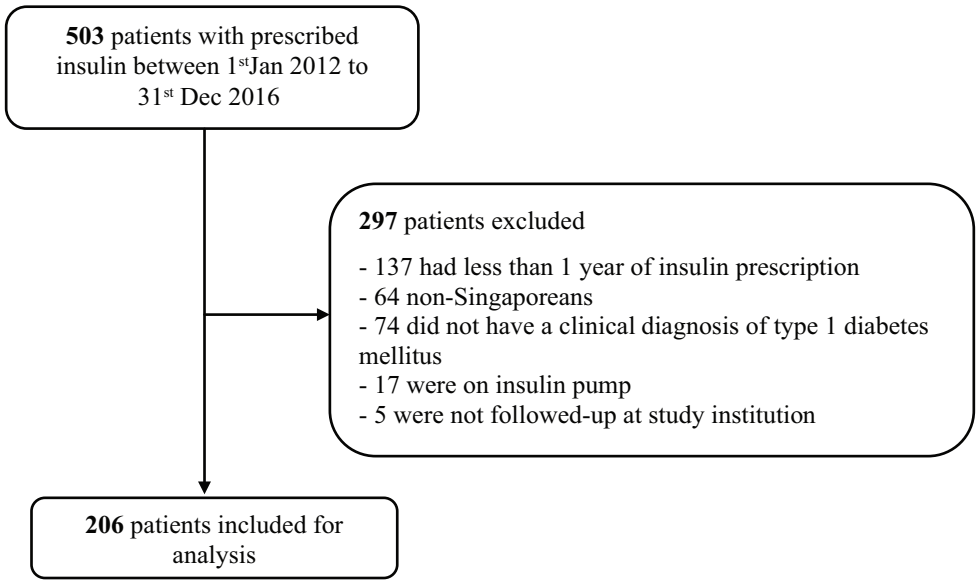

Fig. 1: Flow diagram of the selection of patients for the study

Table 1: Baseline characteristics of the study cohort

Patient characteristics	Adherent (MPR=100%), n=136	Non-adherent (MPR <100%), n=70	p-value
Patient age (years), mean (SD)	11.6 (3.7)	12.4 (4.1)	0.001
Male gender, n (%)	65 (47.8)	38 (54.3)	0.377
Pubertal status, n (%)			
Pre-pubertal	60 (44.1)	26 (37.1)	0.581
Pubertal	75 (55.2)	43 (61.5)	
Post-pubertal	1 (0.7)	1 (1.4)	
Race, n (%)			
Chinese	97 (71.3)	44 (62.9)	0.073
Malay	24 (17.6)	9 (12.9)	
Indian	13 (9.6)	13 (18.6)	
Others	2 (1.5)	4 (5.7)	
BMI category#, n (%)			
Underweight	9 (7.2)	7 (11.1)	0.434
Acceptable	105 (84.0)	53 (84.1)	
Overweight	11 (8.8)	3 (4.8)	
Engaged with exercise^			
Yes	93 (68.4)	42 (60.0)	0.231
No	43 (31.6)	28 (40.0)	
Self-monitoring of blood glucose			
Yes	134 (98.5)	66 (94.3)	0.183
No	2 (1.5)	4 (5.7)	
BMI Z-score#, mean (SD)	−0.211 (0.95)	−0.252 (0.95)	0.782
Diabetes diagnosis duration (years), mean (SD)	2.6 (3.3)	4.7 (4.3)	0.001
Financial class, n (%)			
Subsidized	114 (83.8)	61 (87.1)	0.528
Non-subsidized	22 (16.2)	9 (12.9)	
Number of concurrent medications, mean (SD)	0.35 (0.79)	0.44 (0.79)	0.442
Comorbidities present			
Yes	24 (17.6)	15 (21.4)	0.512
No	112 (82.4)	55 (78.6)	
Number of daily injections, mean (SD)	4.4 (0.83)	4.4 (0.69)	0.871
Duration of follow-up from index visit (years), mean (SD)	3.6 (1.2)	3.2 (1.2)	0.035

#Excludes 18 patients as there is no Singapore BMI for age percentile chart for children <6 years old, ^Based on patient or caregiver reports during clinic visits regarding exercise involvement. BMI: Body mass index, MPR: Medication possession ratio

Association between non-adherence and glycemic control

Table 3 summarizes the association between glycemic control and non-adherence. Patients in the non-adherent group had a higher average HbA1c compared with patients in the non-adherent group when adjusted for age, duration of diabetes, duration of follow-up, pubertal status, exercise, and self-monitoring of blood glucose (mean [SD] 9.6% [2.1] vs. 8.6% [1.3], respectively, p<0.001). A similar relationship was also observed for the varying MPR thresholds during sensitivity analyses. In addition, a smaller decrease in HbA1c among patients who were non-adherent compared with patients who were adherent was observed, although this was not statistically significant (mean [SD] -1.0% [2.5] vs -1.3% [6.7]; p= 0.864). This was also observed at a MPR threshold of 95%, but not for 80%.

Association between non-adherence and health-care utilization

The association between non-adherence and outpatient visits, inpatient visits, and emergency department visits is displayed in Tables 4-6, respectively. There was no significant association between non-adherence and outpatient visits, emergency visits, and inpatient admissions at a MPR threshold of 100% when adjusted for age, gender, race, financial class, and duration of diabetes since diagnosis, number of concurrent medications, number of injections daily, and average HbA1c. Similarly, there was no significant association between non-adherence and health-care utilization when the MPR threshold was set to 95%. However, at a threshold of 80%, non-adherence was associated with 41.2% (rate ratio=0.59, 95% CI: 0.37–0.94, p=0.027) and 37.6% (rate ratio= 0.62, 95% CI: 0.42–0.93, p=0.020) decreased incidence of all-cause hospitalization and all-cause emergency visits, respectively. This was not observed for outpatient visits, or diabetes-related hospital admissions and emergency visits.

Factors associated with non-adherence

The factors associated with non-adherence are reflected in Table 7. Patients who had diabetes for more than 5 years were 2.1 times (odds ratio=2.17, 95% CI: 1.01–4.64, p=0.047), more likely to be non-adherent compared with those with 5 or less years of the disease. In addition, patients were 1.5 times (odds ratio=1.50, 95% CI: 1.20–1.87, p<0.001), more likely to be non-adherent with every 1% increase in average HbA1c. Non-adherence was not associated with adolescent age, gender, race, financial class, presence of comorbidities, exercise, monitoring of blood glucose, and number of daily injections.

Table 2: Sensitivity analyses for the prevalence of non-adherence

Medication possession ratio threshold (%)	Adherent (n)	Non-adherent (n)	Prevalence of non-adherence (95% CI)
100	136	70	34.0 (27.9–40.7)
95	154	52	25.2 (19.8–31.6)
80	183	23	11.2 (7.6–16.2)

In sensitivity analyses, average HbA1c remained a significant factor associated with non-adherence at all MPR thresholds. In addition, at the MPR threshold of 95%, with more than 5 years of diabetes since diagnosis were 3 times (odds ratio=3.00, 95% CI: 1.34–6.74, p=0.008), more likely to be non-adherent.

DISCUSSION

Insulin therapy is fundamental in the management of T1DM, with non-adherence associated with multiple complications and increased costs to the health-care system. Although the use of pharmacy refill records as a measure of adherence is common among adult patients with diabetes [6], information on its use among pediatric patients with T1DM remains scarce [14]. To date, this study is the largest study using

Table 3: Association of non-adherence and glycemic control

Medication possession ratio threshold (%)	Hemoglobin A1c (%), mean (SD)	Adherent	Non-adherent	p-value*
100	Index visit	10.3 (3.1)	10.3 (2.6)	0.460
	Last visit	9.0 (5.9)	9.3 (2.0)	0.556
	Change since the index visit	−1.3 (6.7)	−1.0 (2.5)	0.864
	Average in follow-up period	8.6 (1.3)	9.6 (2.1)	<0.001
95	Index visit	10.2 (3.0)	10.6 (2.6)	0.089
	Last visit	8.9 (5.6)	9.7 (2.0)	0.282
	Change since the index visit	−1.2 (6.3)	−0.9 (2.7)	0.886
	Average in follow-up period	8.7 (1.4)	9.8 (2.0)	<0.001
80	Index visit	10.2 (2.9)	11.0 (2.6)	0.156
	Last visit	9.0 (5.1)	9.8 (2.2)	0.402
	Change since the index visit	−1.1 (5.9)	−1.2 (2.7)	0.948
	Average in follow-up period	8.8 (1.5)	10.0 (2.2)	0.001

*Adjusted for age, diabetes diagnosis duration, duration of follow-up, pubertal status, exercise, and glucose monitoring

Table 4: Association of non-adherence and outpatient visits

Medication possession ratio threshold (%)	Visit type	Adherence category	Rate per patient-year	Adjusted rate ratio*	95% confidence interval	p-value
100	Endocrine	Adherent	4.27	Reference	0.93–1.10	0.788
		Non-adherent	4.34	1.01		
	Diabetes related	Adherent	5.13	Reference	0.92–1.07	0.891
		Non-adherent	5.14	1.00		
	All-cause	Adherent	5.47	Reference	0.91–1.05	0.571
		Non-adherent	5.41	0.98		
95	Endocrine	Adherent	4.26	Reference	0.96–1.15	0.313
		Non-adherent	4.40	1.05		
	Diabetes related	Adherent	5.11	Reference	0.95–1.12	0.478
		Non-adherent	5.26	1.03		
	All-cause	Adherent	5.44	Reference	0.93–1.09	0.835
		Non-adherent	5.51	1.01		
80	Endocrine	Adherent	4.26	Reference	0.93–1.19	0.384
		Non-adherent	4.55	1.06		
	Diabetes related	Adherent	5.13	Reference	0.91–1.14	0.800
		Non-adherent	5.27	1.02		
	All-cause	Adherent	5.43	Reference	0.91–1.14	0.729
		Non-adherent	5.68	1.02		

*Adjusted for age, gender, race, financial class, duration of diabetes diagnosis, presence of comorbidities, number of daily injections, and average HbA1c.
HbA1c: Hemoglobin A1c

Table 5: Association of non-adherence and inpatient visits

Medication possession ratio threshold (%)	Visit type	Adherence category	Rate per patient-year	Adjusted rate ratio*	95% confidence interval	p-value
100	Diabetes related	Adherent	0.19	Reference	0.87–1.90	0.214
		Non-adherent	0.27	1.28		
	All-cause	Adherent	0.40	Reference	0.63–1.15	0.288
		Non-adherent	0.39	0.85		
95	Diabetes related	Adherent	0.19	Reference	0.99–2.22	0.054
		Non-adherent	0.29	1.49		
	All-cause	Adherent	0.38	Reference	0.78–1.45	0.710
		Non-adherent	0.43	1.06		
80	Diabetes related	Adherent	0.22	Reference	0.39–1.27	0.236
		Non-adherent	0.19	0.70		
	All-cause	Adherent	0.41	Reference	0.37–0.94	0.027
		Non-adherent	0.30	0.59		

*Adjusted for age, gender, race, financial class, duration of diabetes diagnosis, presence of comorbidities, number of daily injections, and average HbA1c.
HbA1c: Hemoglobin A1c

pharmacy refill records as a measure of adherence among pediatric patients with T1DM. The study has shown a prevalence of non-adherence of 34.0%, which is associated with poorer glycemic control.

Similarly, Morris *et al*. (Scotland) reported an inverse relationship between adherence and HbA1c among 89 adolescent patients with T1DM [11]. Adherence, expressed as a continuous variable in days of insulin coverage per annum, was comparable to this study's definition with a MPR threshold of 100%. Up to 28.1% of the patients collected <1 year of insulin. However, the adherence index was inversely associated with hospitalization due to diabetes, which was not consistent with the results of this study. This could be due to the low hospitalization rates in the present study cohort that is insufficiently powered to detect a significant difference. Another study utilizing pharmacy refill records by Ying *et al*. (Malaysia) involving 57 pediatric patients with T1DM, reported a prevalence of non-adherence of 31.6%

Table 6: Association of non-adherence and emergency visits

Medication possession ratio threshold (%)	Visit type	Adherence category	Rate per patient-year	Adjusted rate ratio*	95% confidence interval	p value
100	Diabetes related	Adherent	0.19	Reference	0.91–1.97	0.146
		Non-adherent	0.29	1.33		
	All-cause	Adherent	0.59	Reference	0.64–1.06	0.134
		Non-adherent	0.53	0.83		
95	Diabetes related	Adherent	0.20	Reference	0.93–2.07	0.113
		Non-adherent	0.29	1.38		
	All-cause	Adherent	0.58	Reference	0.72–1.22	0.683
		Non-adherent	0.54	0.94		
80	Diabetes related	Adherent	0.23	Reference	0.38–1.23	0.203
		Non-adherent	0.19	0.68		
	All-cause	Adherent	0.59	Reference	0.42–0.93	0.020
		Non-adherent	0.42	0.62		

*Adjusted for age, gender, race, financial class, duration of diabetes diagnosis, presence of comorbidities, number of daily injections, and average HbA1c.
HbA1c: Hemoglobin A1c

Table 7: Factors associated with non-adherence

Medication possession ratio threshold (%)	Predictors	Odds ratio	95% confidence interval	p-value
100	Age (years)			
	1 to 9 (Non-adolescent)	Reference	0.71–3.34	0.270
	10 to 18 (Adolescent)	1.54		
95	Age (years)			
	1 to 9 (Non-adolescent)	Reference	0.53–3.02	0.595
	10 to 18 (Adolescent)	1.27		
80	Age (years)			
	1 to 9 (Non-adolescent)	Reference	0.32–3.59	0.902
	10 to 18 (Adolescent)	1.08		
100	Gender			
	Male	Reference	0.26–1.01	0.055
	Female	0.51		
95	Gender			
	Male	Reference	0.26–1.13	0.102
	Female	0.54		
80	Gender			
	Male	Reference	0.22–1.57	0.288
	Female	0.59		
100	Race			
	Non-Chinese	Reference	0.36–1.48	0.382
	Chinese	0.73		
95	Race			
	Non-Chinese	Reference	0.39–1.83	0667
	Chinese	0.84		
80	Race			
	Non-Chinese	Reference	0.31–2.34	0.762
	Chinese	0.86		
100	Financial class			
	Non-subsidized	Reference	0.68–5.58	0.212
	Subsidized	1.95		
95	Financial class			
	Non-subsidized	Reference	0.91–12.90	0.070
	Subsidized	3.42		
80	Financial class			
	Non-subsidized	Reference	0.23–3.51	0.884
	Subsidized	0.90		
100	Diabetes diagnosis duration (years)			
	≤ 5 years	Reference	1.01–4.64	0.047
	> 5 years	2.17		
95	Diabetes diagnosis duration (years)			
	≤ 5 years	Reference	1.34–6.74	0.008
	> 5 years	3.00		
80	Diabetes diagnosis duration (years)			
	≤ 5 years	Reference	0.77–6.22	0.140
	> 5 years	2.19		
100	Presence of comorbidity			
	Yes	0.65	0.28–1.54	0.330
	No	Reference		

(Contd...)

Table 7: ***(Continued)***

Medication possession ratio threshold (%)	Predictors	Odds ratio	95% confidence interval	p-value
95	Presence of comorbidity			
	Yes	0.97	0.40–2.35	0.948
	No	Reference		
80	Presence of comorbidity			
	Yes	1.05	0.33–3.35	0.935
	No	Reference		
100	Engaged with exercise^			
	Yes	0.61	0.31–1.19	0.147
	No	Reference		
95	Engaged with exercise^			
	Yes	0.60	0.29–1.24	0.164
	No	Reference		
80	Engaged with exercise^			
	Yes	1.61	0.56–4.61	0.379
	No	Reference		
100	Self-monitoring of blood glucose			
	Yes	0.20	0.02–1.52	0.119
	No	Reference		
95	Self-monitoring of blood glucose			
	Yes	1.89	0.16–22.21	0.616
	No	Reference		
80	Self-monitoring of blood glucose			
	Yes	0.81	0.07–9.79	0.870
	No	Reference		
100	Number of daily injections	1.16	0.75–1.82	0.505
95	Number of daily injections	0.91	0.56–1.47	0.688
80	Number of daily injections	0.87	0.50–1.52	0.625
100	Average HbA1c (%)	1.50	1.20–1.87	<0.001
95	Average HbA1c (%)	1.58	1.22–1.93	<0.001
80	Average HbA1c (%)	1.46	1.12–1.94	0.008

^Based on patient or caregiver reports during clinic visits regarding exercise involvement. HbA1c: Hemoglobin A1c

using a MPR threshold of 80%, which differed from the present study's result of 11.2% [12]. Possible reasons could include the differences in health-care financing and closer proximity of health-care services in Singapore to residential areas, which encourages routine follow-up and collection of medications by patients. Further comparisons with the study were not possible as HbA1c was used as a measure of non-adherence for further analyses instead of the MPR.

Non-adherence was associated with poorer glycemic control, with a 50% increased risk with every 1% increase in average HbA1c. While non-adherence has been associated with poorer glycemic control among pediatric patients with T1DM [15], the adherence measures largely involved the use of glucometer data and patient surveys instead of pharmacy refill records. Hence, this study adds to the current body of evidence pertaining to the relationship between non-adherence and poor glycemic control. In addition, patients with longer disease vintage were more likely to be non-adherent to insulin therapy. This is consistent with other studies and could possibly be attributed to treatment fatigue [16]. Hence, this may prompt clinicians to pay closer attention to this group of patients and assess their adherence more frequently. Contrary to existing studies reporting poor treatment adherence among adolescents [14], this study did not observe a similar relationship. A possible reason for this discrepancy in findings could due to an inadequate sample size, which is underpowered to detect a significant difference.

A MPR threshold of <100% was used to define non-adherence in the present study with sensitivity analyses performed at 95% and 80%. Sensitivity analyses for different MPR thresholds consistently showed a significant association of non-adherence and poorer glycemic control across all thresholds. In terms of health-care utilization, a significant association was not observed at a threshold of 100% possibly due to the low event rates in the study population to detect a statistically significant different. Although a paradoxical relationship was observed between non-adherence and all-cause hospitalization and emergency visits at a MPR threshold of 80%, the results should be interpreted with caution, given the a small number of non-adherent patients (n=23). While there are no formal recommendations for the definition of non-adherence, a threshold of <80% is often regarded as poor adherence [17]. However, higher MPR thresholds may be required, depending on the condition, medication, or patient populations [18,19]. For example, a threshold of 95% has been set for antiretroviral therapy due to its association with maximal viral load suppression and minimal opportunistic infection [20]. In the context of T1DM, a MPR threshold of 95% and 80% would represent approximately 18 days and 73 days per annum without insulin, respectively. Although the MPR is unable to provide information on the distribution of days without insulin supply, a single day without insulin in the context of T1DM may be potentially lethal. Hence, a MPR threshold of 100% was used in this study, although it may appear too idealistic to be achieved in clinical practice.

The study should be interpreted in light of the following limitations. First, as with other studies using retrospective databases, the presence of medication refill is not equivalent to the consumption of medications by patients. Despite that, pharmacy refill records continue to be widely used as an objective measure of adherence. Second, health-care utilization and MPR may be underestimated as patients may visit community physicians and pharmacies closer to their residential areas. Visit information and refill records from these health-care centers would not be captured in this study. However, given that study institute is the largest pediatric hospital where government subsidies are available for Singaporeans, the impact of collection from other health-care centers is likely minimal. Third, insulin adjustments which may follow different diet plans, and involvement of caregivers were not accounted for in the present study. Since MPR measures only a single adherence behavior in the implementation phase of adherence time continuum [18], patient-reported measures such as the Diabetes Self-Management Profile and diabetes self-care activities can be used concurrently with pharmacy refill records to provide holistic insights into non-adherent behaviors.

CONCLUSION

More than 30% of pediatric patients in Singapore with T1DM are non-adherent to insulin therapy, which is associated with poorer glycemic control. Further interventions need to be developed to address this need, especially for those who has had diabetes for more than 5 years. While pharmacy refill records may serve as a measure of adherence among pediatric patients with T1DM, an appropriate MPR threshold for adherence remains to be determined. In addition, further studies can be done to explore the effects of pharmacy refill records in conjunction with patient-reported outcomes to provide a holistic picture of non-adherent behaviors.

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AUTHORS' CONTRIBUTIONS

Chua Wen Bing Brandon was involved in the study conception and design, analysis and interpretation of data, drafting and reviewing of manuscript. Lim Xin Yan and Poh Kar Men were involved in the analysis and interpretation of data, drafting of manuscript. Jamie Stephanie Caleb was involved in the study conception and design, drafting of the manuscript. McVin Cheen Hua Heng, Lim Soo Ting, and Lek Ngee were involved in the study design and methodology, reviewed, and approved manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare. No funding was provided for the conduction of this study.

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