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Type 1 diabetes management and outcomes: A multicenter study in Thailand

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ABSTRACT

Aims/Introduction: The Thai Type 1 Diabetes and Diabetes Diagnosed Before Age 30 Years Registry, Care and Network was established in 2014 and involved 31 hospitals. The objective of the registry was to evaluate glycemic control and complications of patients with type 1 diabetes.

Materials and Methods: Patients' demographics, clinical data, frequencies of daily self-monitoring of blood glucose (SMBG), glycemic control and complications were collected.

Results: Among the 1,907 type 1 diabetes patients, the mean age was 21.2 ± 11.3 years. The mean glycated hemoglobin level was 9.35 ± 2.41%, with significant variations among age groups ($P < 0.001$). Conventional insulin treatment and intensive insulin treatment were used in 43 and 57% of patients, respectively. Mean glycated hemoglobin levels were significantly higher in patients treated with conventional insulin treatment compared to those treated with intensive insulin treatment (9.63 ± 2.34 vs 9.17 ± 2.46%, $P = 0.002$). Compared to the conventional insulin treatment group, significantly more patients in the intensive insulin treatment group achieved good glycemic control ($P < 0.001$), and fewer had diabetic retinopathy ($P = 0.031$). The prevalence of microvascular complications increased significantly with age ($P < 0.001$). Multivariate analysis showed good glycemic control to be associated with age 25 to <45 years, intensive insulin treatment with SMBG three or more times daily and diabetes duration of 1 to <5 years.

Conclusions: Most Thai type 1 diabetes patients were not meeting the recommended glycemic target. As a result of this study, the national program to improve the quality of diabetes treatment and education has been implemented, and the results are ongoing.

[†]The members of T1DDAR CN are listed in Appendix 1

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INTRODUCTION

Thailand is an upper-middle income developing country that has provided universal health coverage for its entire population since 2002 through the implementation of three health insurance programs, including: (i) the Civil Servant Medical Benefit Scheme for government officials and their dependents; (ii) the Social Security Scheme for private sector employees; and (iii) the Universal Health Coverage Scheme for the remaining population not covered by the Civil Servant Medical Benefit Scheme or Social Security Scheme[1]. In Thailand, universal health coverage benefits include the majority of medicines, investigations and medical equipment, but it excludes high-cost investigations and treatments. For diabetes treatment, self-monitoring of blood glucose (SMBG), continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring are not covered, so the costs of these important evaluation and treatment modalities place a significant financial burden on individuals living with type 1 diabetes. Difficult access to insulin analogs, and the shortage of knowledgeable healthcare professionals to provide diabetes self-management education and support (DSMES) are also important obstacles to intensive insulin treatment (IIT) for type 1 diabetes in Thailand. The inability of parents and schools to provide support are also important barriers to IIT among children with type 1 diabetes in Thailand. As a consequence of these barriers to patient care and education, conventional insulin treatment (CIT) is a common treatment among Thai type 1 diabetes patients that are indicated for IIT. These obstacles, both individually and collectively, prevent the optimal management of type 1 diabetes patients in Thailand.

The incidence of type 1 diabetes is increasing globally[2]. This has also been observed in Thailand[3–7]. The incidence of type 1 diabetes among children aged 0–15 years in Thailand was increased from 0.2 per 100,000/year in 1984–1985 to 1.65 per 100,000/year in 1991–1995[5]. In 2003, the Thailand Diabetes Registry Project reported the prevalence of type 1 diabetes diagnosed before the age of 18 years to be 2.07% from 11 tertiary centers[8]. Data on type 1 diabetes in Thailand have been lacking since 2003. Established in 2014, the Thai Type 1 Diabetes and Diabetes Diagnosed Before Age 30 Years Registry, Care and Network (T1DDAR CN) is a collaboration among the Thai Society for Pediatric Endocrinology, the Endocrine Society of Thailand and the Diabetes Association of Thailand; government entities, such as the Siriraj Diabetes Center, Faculty of Medicine Siriraj Hospital, Mahidol University; the Northern Diabetes Center, Faculty of Medicine, Chiang Mai University; and the National Health Security Office (NHSO) of Thailand. The current network covers 31 hospitals around Thailand. Due to limited resource setting for type 1 diabetes and young-onset diabetes patients in Thailand, T1DDAR CN had the following objectives: (i) to strengthen the clinical knowledge of medical professionals; (ii) to develop a referral system and network for IIT and specific DSMES program; (iii) to create DSMES teaching modules and education materials that focus on both survival skills and continuing education in simple and easy-to-use Thai language; and, (iv) to initiate cohort data of type 1 diabetes patients of all ages, and of patients who were diagnosed with diabetes before the age of <30 years.

The objectives of the present study were to assess glycemic control and diabetes complications in patients enrolled in the database of T1DDAR CN, and to determine factors associated with good glycemic control among patients with type 1 diabetes in Thailand.

METHODS

Data of type 1 diabetes patients from 31 T1DDAR CN network hospitals (see Appendix 1) diagnosed during January 2005–2016 were retrospectively reviewed. The T1DDAR CN network hospitals are tertiary care level, with healthcare professionals who are interested in strengthening the education/support team for their type 1 diabetes patients. These hospitals function as referral centers for local hospitals located within their referral area. An electronic case record form was developed using Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA), which is a web-based program. REDCap is hosted by the Research Institute for Health Sciences of Chiang Mai University, Chiang Mai, Thailand. Siriraj Diabetes Center together with Research Institute for Health Sciences operates as the administrative and data coordination center of the T1DDAR CN study. The researchers and research coordinators from each participating center received training in an effort to standardize data collection. Written instruction in how to complete the electronic case record form was also provided. The researchers and research coordinators had secure sign-in authorization, and they could only access their own data. Data were collected at each site during September 2015 to March 2016. Data entry activities were closely monitored and reviewed monthly by the data coordinators and the principal investigators.

Data, including characteristics, treatment, glycemic control, daily SMBG, acute diabetic complications (including diabetic ketoacidosis [DKA] and severe hypoglycemia) and chronic diabetic complications (including diabetic retinopathy, diabetic nephropathy and diabetic neuropathy), were retrospectively reviewed. Obesity was considered if the patients had a body mass index of ≥25 kg/m^2 for those aged >18 years or weight for height of ≥140% for those aged <18 years. Dyslipidemia was diagnosed if low density lipoprotein cholesterol was >100 mg/dL or the patients were receiving hyperlipidemia treatment. Hypertension was defined if the patients had elevated blood pressure or were treated with antihypertensive medication. Diabetic retinopathy was defined if the patients had macular edema, proliferative or non-proliferative

retinopathy, vitreous hemorrhage, or tractional retinal detachment. Diabetic nephropathy was considered if persistent albuminuria (>30 mg/g creatinine) was identified. Diabetic neuropathy was diagnosed by monofilament examination, loss of reflex or loss of vibratory sensation.

To assess glycemic control, treatment regimen and the prevalence of complications among different age groups, patients were stratified into seven age groups, similarly to the previous studies: the Australasian Diabetes Data Network[9] and the study of Type 1 Diabetes Exchange clinic registry[10]. Insulin regimen was categorized as follows: CIT (premixed or self-mixed insulin 1–3 injections per day) and IIT (multiple daily injections ≥4 injections per day or CSII).

Glycemic control was classified as: (i) good glycemic control: glycated hemoglobin (HbA_{1c}) <7.5% in the <18 years age group, and <7.0% in the ≥18 years age group; (ii) fair glycemic control: HbA_{1c} within the range of 7.5–9.0% in the <18 years age group, and within the range of 7.0–9.0% in the ≥18 years age group; and (iii) poor glycemic control: HbA_{1c} >9% in all age groups.

The study protocol was approved by the Central Research Ethics Committee of Thailand (approval number CREC 009/2559- Bm), and each participating site obtained local institutional board approval.

Statistical analysis

Data analysis was carried out using Stata/IC version 14.0 for Windows (StataCorp LP, College Station, TX, USA). Patients with missing data were omitted from the analyses involving that variable, but were included in the rest of the study. For normally distributed variables, data are presented as the number and percentage for categorical data, and as the mean ± standard deviation for continuous data. For non-normally distributed continuous variables, data are presented as the median and interquartile range. For comparison between groups, Student's *t*-test, Mann–Whitney *U*-test, weighted analysis of variance (ANOVA), *F*-test and Kruskal–Wallis test were used for continuous variables, as appropriate. The χ^2-test was used to compare categorical variables, and Scheffé's method was used for multiple comparisons. Logistic regression analysis was carried out to identify independent predictors of optimal glycemic control. Only patients with a duration of type 1 diabetes of >1 year were included. Achievement of HbA_{1c} targets (HbA_{1c} <7.5% in the <18 years age group and <7.0% in the ≥18 years age group) was entered as the dependent variable. Potential factors associated with glycemic target achievement, including age, duration of disease, sex, health insurance schemes, educational level, insulin regimen and frequency of SMBG, were analyzed in univariate analysis. Factors identified as significant in univariate analysis were entered into multivariate logistic regression analysis. The household income per month was not included in the logistic regression analysis because of a high percentage of missing values (32.8%). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A cohort of 1,907 type 1 diabetes patients (778 males/1,129 females), with a mean age at diagnosis of 13.5 ± 9.2 years, a current mean age of 21.2 ± 11.3 years and a mean duration of disease of 7.7 ± 6.4 years, were included and analyzed (Table 1). Notably, just 3.17 and 3.54% of the patients were in the age groups of <6 years and ≥45 years, respectively. Just 13

Table 1 | Characteristics of the 1,907 type 1 diabetes patients included in this study

Characteristics	*n*	Value
Current age (years)	1,907	21.2 ± 11.3
Age at diagnosis (years)	1,892	13.5 ± 9.2
Duration of type 1 diabetes (years)	1,868	7.7 ± 6.4
Sex (female)	1,907	1129 (59.2%)
Health insurance schemes	1,900	
Civil servant medical benefit scheme		249 (13.1%)
Social security scheme		192 (10.1%)
Universal health coverage scheme		1280 (67.4%)
Others		179 (9.4%)
Household income per month	1,191	
<$300		272 (22.8%)
$300 to <600		412 (34.6%)
$600 to <900		216 (18.1%)
$900 to <1,500		152 (12.8%)
≥$1,500		139 (11.7%)
Mean HbA_{1c} (%)	1,820	9.35 ± 2.41
Good glycemic control		293 (16.1%)
Fair glycemic control		668 (36.7%)
Poor glycemic control		859 (47.2%)
Frequency of SMBG (mean ± SD)	1,687	2.06 ± 1.41
≤1/day		659 (39.1%)
2/day		350 (20.8%)
3/day		337 (20.0%)
≥4/day		341 (20.2%)
Comorbidity	1,897	
Obesity		131 (6.9%)
Dyslipidemia		523 (27.6%)
Hypertension		173 (9.1%)
Prevalence of DKA per year	1,815	186 (10.2%)
Prevalence of severe hypoglycemia per year	1,638	140 (8.5%)
Diabetic retinopathy	1,339	142 (10.6%)
Diabetic nephropathy	1,330	305 (22.9%)
Diabetic neuropathy	577	30 (5.2 %)

Data presented as number and percentage or mean ± standard deviation. Income is shown in US dollars. Good glycemic control: glycated hemoglobin (HbA_{1c}) <7.5% in the <18 years age group, and <7.0% in the ≥18 years age group; fair glycemic control: HbA_{1c} within the range of 7.5–9.0% in the <18 years age group, and within the range of 7.0–9.0% in the ≥18 years age group; and, poor glycemic control: HbA_{1c} >9% in all age groups. DKA, diabetic ketoacidosis; SBMG, self-monitoring of blood glucose.

Table 2 | Participant characteristics stratified by age group

	Total	Age group (years)							
	(*n* = 1,892)	<6 (*n* = 60)	6 to <10 (*n* = 146)	10 to <14 (*n* = 314)	14 to <18 (*n* = 353)	18 to <25 (*n* = 462)	25 to <45 (*n* = 490)	≥45 (*n* = 67)	*P*-value
Sex (female)	1,121 (59.2%)	30 (50.0%)	80 (54.8%)	192 (61.2%)	208 (58.9%)	270 (58.4%)	301 (61.4%)	40 (59.7%)	0.556
Duration of disease (years)	1,861	1 (0–2)	0 (1–4)	3 (1–5)	5 (3–8)	8 (4–11)	10 (5–16)	19 (10–27)	<0.001*
HbA_{1c} (%)	1,820	8.98 ± 1.90	9.20 ± 1.88	9.54 ± 2.21	9.89 ± 2.60	9.63 ± 2.68	8.85 ± 2.29	8.03 ± 1.26	<0.001*
Good glycemic control		13 (22.0%)	19 (13.5%)	47 (15.4%)	62 (18.1%)	57 (12.9%)	85 (18.4%)	10 (14.9%)	<0.001*
Fair glycemic control		21 (35.6%)	58 (41.1%)	89 (29.1%)	84 (24.6%)	162 (36.6%)	205 (44.3%)	49 (73.1%)	
Poor glycemic control		25 (42.4%)	64 (45.4%)	170 (55.6%)	196 (57.3%)	223 (50.4%)	173 (37.4%)	8 (11.9%)	
Insulin regimen	1,862								
Conventional treatment		30 (50.0%)	88 (60.3%)	149 (48.4%)	149 (42.8%)	180 (39.6%)	208 (43.3%)	18 (27.3%)	0.001*
Intensive treatment		30 (50.0%)	58 (39.7%)	159 (51.6%)	199 (57.2%)	274 (60.4%)	272 (56.7%)	48 (72.7%)	
Basal–bolus regimen		29 (48.3%)	58 (39.7%)	155 (50.3%)	197 (56.6%)	267 (58.8%)	266 (55.4%)	48 (72.7%)	
Continuous subcutaneous insulin infusion		1 (1.7%)	0 (0.0%)	4 (1.3%)	2 (0.6%)	7 (1.5%)	6 (1.2%)	0 (0.0%)	
SMBG	1,687	3 (2–4)	3 (2–4)	3 (2–4)	2 (1–3)	2 (1–3)	1 (0–2)	2 (1–3)	
≤1/day		9 (17.0%)	25 (18.1%)	67 (22.7%)	111 (33.6%)	201 (49.1%)	226 (55.7%)	20 (35.7%)	<0.001*
2/day		11 (20.8%)	23 (16.7%)	50 (17.0%)	82 (24.8%)	87 (21.3%)	83 (20.4%)	14 (25.0%)	
3/day		12 (22.6%)	39 (28.3%)	88 (29.8%)	71 (21.5%)	62 (15.2%)	53 (13.0%)	12 (21.4%)	
≥4/day		21 (39.6%)	51 (37.0%)	90 (30.5%)	66 (20.0%)	59 (14.4%)	44 (10.8%)	10 (17.9%)	
Prevalence of DKA per year	1,815	3 (5.1%)	8 (5.6%)	45 (14.6%)	38 (11.0%)	58 (13.2%)	31 (6.8%)	3 (4.6%)	0.001*
Prevalence of severe hypoglycemia per year	1,638	3 (5.3%)	10 (7.0%)	20 (6.6%)	19 (5.5%)	35 (8.1%)	44 (10.1%)	9 (14.3%)	0.105
Diabetic retinopathy	1,339	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (6.1%)	98 (25.4%)	24 (40.0%)	<0.001*
Diabetic nephropathy	1,330	0 (0.0%)	5 (9.4%)	15 (7.8%)	47 (17.5%)	90 (25.6%)	123 (31.6%)	25 (41.0%)	<0.001*
Diabetic neuropathy	577	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.2%)	16 (6.1%)	10 (33.3%)	<0.001*

Data presented as number and percentage, median and interquartile range or mean ± standard deviation. *A *P*-value <0.05 shows statistical significance. Good glycemic control: glycated hemoglobin (HbA_{1c}) <7.5% in the <18 years age group, and <7.0% in the ≥18 years age group; fair glycemic control: HbA_{1c} within the range of 7.5–9.0% in the <18 years age group, and within the range of 7.0–9.0% in the ≥18 years age group; and poor glycemic control: HbA_{1c} >9% in all age groups. DKA, diabetic ketoacidosis; SBMG, self-monitoring of blood glucose.

patients were aged ≥65 years; thus, they were categorized into the ≥45 years age group (Table 2). Regarding health insurance schemes, the majority of patients (67.4%) had Universal Health Coverage Scheme, 13.1% had Civil Servant Medical Benefit Scheme and 10.1% were covered by Social Security Scheme. More than half of patient families (57.4%) had a monthly household income <$600, and 30.9% of families earned $600–<1,500 per month. Just 11.7% had a monthly household income ≥$1,500. Obesity, dyslipidemia and hypertension were identified in 6.9, 27.6 and 9.1% of patients, respectively (Table 1). The prevalence of autoimmune thyroid disease was 5.2%.

Glycemic control

The mean HbA_{1c} level was 9.35 ± 2.41%, and mean HbA_{1c} levels varied significantly according to age ($P < 0.001$; Figure 1a). HbA_{1c} levels gradually increased from 8.98 ± 1.90% in the <6 years age group to the highest level of 9.89 ± 2.60% in the 14 to <18 years age group. The lowest level of 8.03 ± 1.26% was observed in the ≥45 years age group (Table 2; Figure 1a). Good glycemic control was achieved in just 16.1% of patients (Table 1). The percentage of patients achieving HbA_{1c} targets was lowest (12.9%) in the 18 to <25 years age group, and highest (22.0%) in the <6 years age group. The percentage of poor glycemic control was highest in the 14 to <18 years age group (57.3%), and lowest in the ≥45 years age group (11.9%; Figure 1b).

SMBG

The mean frequency of SMBG was 2.06 ± 1.41 times daily. A higher frequency of SMBG was found to be significantly associated with lower HbA_{1c} levels ($P < 0.001$; Figure 2). Multiple comparisons (Scheffé's method) showed that SMBG carried out four times daily was significantly associated with lower HbA_{1c} compared with SMBG one or fewer to three times daily (SMBG four times daily vs SMBG three times daily [$P = 0.032$], SMBG four times daily vs SMBG two times daily ($P = 0.001$), SMBG four times daily vs SMBG ≤1 time daily [$P < 0.001$]). However, individuals carrying out SMBG three times daily had similar levels of HbA_{1c} to those who carried out SMBG two times daily ($P = 0.684$).

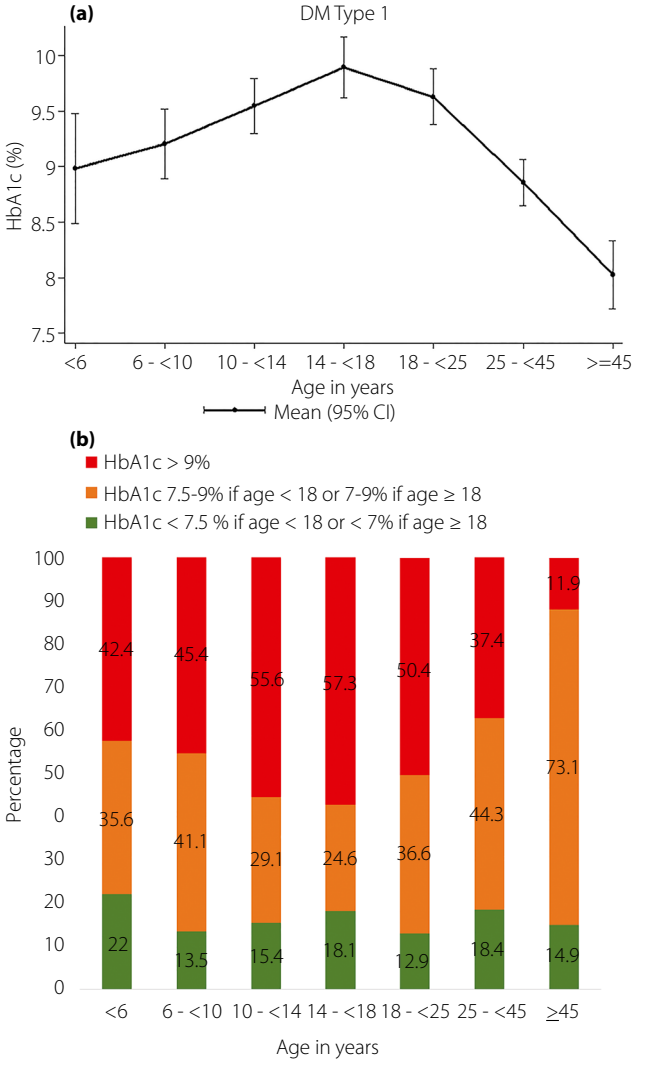

Figure 1 | (a) Mean glycated hemoglobin (HbA1c) of 1,820 patients with type 1 diabetes stratified by age. (b) Percentage of patients achieving HbA_{1c} targets stratified by age group. The HbA_{1c} target for those aged <18 years was <7.5%, and the HbA_{1c} target for those aged ≥18 years was <7.0%. CI, confidence interval; DM, diabetes mellitus.

Insulin regimens and treatment outcomes

A total of 43% of patients were on CIT, and 57% were on IIT (Table 3). CSII was used in only 1.1% of patients. Mean HbA_{1c} levels were significantly higher in patients treated with CIT than in those treated with IIT (9.63 ± 2.34% vs 9.17 ± 2.46%, $P = 0.002$). Just around 19% of patients with IIT achieved optimal glycemic control, and just 13% of patients with CIT reached the HbA_{1c} goal ($P < 0.001$).

The annual incidence of the acute diabetic complications, DKA and severe hypoglycemia, was 10.2 and 8.5%, respectively (Table 1). The prevalence of DKA was highest in the 10 to <14 years age group (14.6%). The prevalence of hypoglycemia was highest in participants aged ≥45 years (14.3%; Table 2).

Diabetic retinopathy, diabetic nephropathy and diabetic neuropathy in this cohort was identified in 10.6, 22.9 and 5.2% of patients, respectively (Table 1). The prevalence of both diabetic retinopathy and diabetic nephropathy increased in our older patients. The prevalence of diabetic retinopathy was 6.1% in the 18 to <25 years age group, it increased to 25.4% in the 25 to <45 years age group, and it further increased to 40% in the ≥45 years age group. The prevalence of diabetic nephropathy was 25.6% in the 18 to <25 years age group, and the prevalence increased with age (41% in the ≥45 years age group). The prevalence of diabetic neuropathy was 2.2% in the 18 to <25 years age group, and it increased to 33.3% in the ≥45 years age group (Table 2). The prevalence of DKA, severe hypoglycemia, diabetic

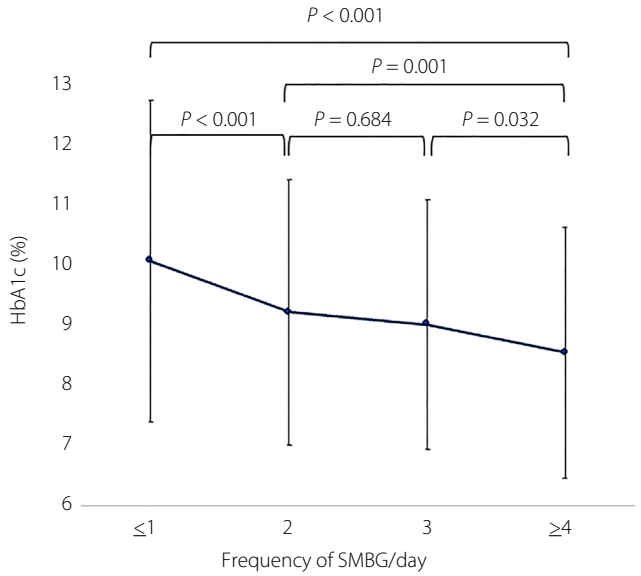

Figure 2 | Frequency of self-monitoring of blood glucose (SMBG) relative to glycated hemoglobin (HbA1c) among patients with type 1 diabetes.

nephropathy and diabetic neuropathy were not significantly different between the two insulin regimens. However, the prevalence of diabetic retinopathy was significantly lower in the IIT group (8.5 vs 12.3%, $P = 0.031$; Table 3).

Factors associated with achievement of HbA_{1c} targets

Associations between patients' characteristics and HbA_{1c} target achievement were explored by univariate and multivariate logistic regression analyses. In univariate analysis, good glycemic control was associated with a current age of 25 to <45 years, other type of health insurance scheme (e.g., self-payment, unknown etc.), finishing a bachelor's or master's degree, IIT with frequency of SMBG three or more times daily and duration of disease 1 to <5 years. Multivariate analysis showed good glycemic control to be associated with current age of 25 to <45 years ($P = 0.030$), IIT and frequency of SMBG three or more times daily ($P < 0.001$), and duration of disease 1 to <5 years ($P = 0.014$; Table 4).

DISCUSSION

The present nationwide study improves our understanding of the current status and influencing factors of glycemic control (e.g., types of insulin regimen, frequency of SMBG, age and

Table 3 | Clinical and biochemical characteristics of patients with type 1 diabetes stratified by insulin regimen

Characteristics	*n* (1,748)	Conventional insulin treatment (*n* = 755)	Intensive insulin treatment (*n* = 993)	*P*-value
Health insurance scheme	1,741			
Civil servant medical benefit scheme		69 (9.2%)	160 (16.2%)	<0.001*
Social security scheme		65 (8.6%)	100 (10.1%)	
Universal health coverage scheme		558 (74.0%)	632 (64.0%)	
Others		62 (8.2%)	95 (9.6%)	
Gender, female	1,748	421 (55.8%)	616 (62.0%)	<0.001*
Age at diagnosis (years)	1,717	12.3 ± 7.8	13.3 ± 9.4	0.023*
Current age (years)	1,733	19.1 ± 10.0	21.5 ± 11.4	<0.001*
Duration of type 1 diabetes (years)	1,714	5.6 (2.5–9.5)	6.2 (3.1–11.9)	0.003*
HbA_{1c} (%)	1,676	9.63 ± 2.34	9.17 ± 2.46	0.002*
Good glycemic control		94 (13.4%)	181 (18.6%)	<0.001*
Fair glycemic control		233 (33.2%)	372 (38.2%)	
Poor glycemic control		375 (53.4%)	421 (43.2%)	
Frequency of SMBG	1,563	2 (1–3)	3 (1–4)	<0.001*
≤1/day		318 (49.3%)	254 (27.7%)	<0.001*
2/day		161 (25.0%)	169 (18.4%)	
3/day		110 (17.0%)	211 (23.0%)	
≥4/day		56 (8.7%)	284 (30.9%)	
Prevalence of DKA	1,677	70 (10.0%)	104 (10.7%)	0.657
Prevalence of severe hypoglycemia	1,646	48 (7.0%)	81 (8.5%)	0.271
Diabetic retinopathy	1,205	59 (12.3%)	62 (8.5%)	0.031*
Diabetic nephropathy	1,204	112 (23.8%)	155 (21.2%)	0.238
Diabetic neuropathy	505	9 (5.4%)	19 (5.6%)	0.951

Data presented as number and percentage, mean ± standard deviation, or median and interquartile range. *A *P*-value <0.05 shows statistical significance. Good glycemic control: glycated hemoglobin (HbA_{1c}) <7.5% in the <18 years age group, and <7.0% in the ≥18 years age group; fair glycemic control: HbA_{1c} within the range of 7.5–9.0% in the <18 years age group, and within the range of 7.0–9.0% in the ≥18 years age group; and poor glycemic control: HbA_{1c} >9% in all age groups. DKA, diabetic ketoacidosis; SBMG, self-monitoring of blood glucose.

Table 4 | Analysis for predictors of metabolic control achievement in patients with type 1 diabetes

Factors	*n*	Achieved metabolic control	Univariate analysis			Multivariate analysis†		
			OR	95% CI	*P*-value	AOR	95% CI	*P*-value
Age (years)								
<6	35	6 (17.1%)	1.39	0.45–3.62	0.487	0.65	0.20–2.10	0.471
6 to <10	106	12 (11.3%)	0.86	0.40–1.71	0.649	0.60	0.27–1.34	0.213
10 to <14	265	37 (14.0%)	1.09	0.67–1.76	0.716	0.86	0.48–1.54	0.603
14 to <18	318	55 (17.3%)	1.40	0.91–2.17	0.108	1.31	0.79–2.19	0.296
18 to <25	393	51 (13.0%)	Ref.			Ref.		
25 to <45	375	74 (19.7%)	1.65	1.10–2.48	0.011*	2.00	1.07–3.76	0.030*
≥45	50	8 (16.0%)	1.28	0.49–2.96	0.554	1.16	0.39–3.48	0.792
Duration of disease (years)								
1 to <5	607	106 (17.5%)	1.45	1.02–2.08	0.031*	1.65	1.11–2.45	0.014*
5 to <10	480	61 (12.7%)	Ref.			Ref.		
10 to <20	364	61 (16.8%)	1.38	0.92–2.07	0.098	1.18	0.74–1.88	0.478
20 to <30	74	12 (16.2%)	1.33	0.62–2.67	0.406	0.94	0.39–2.26	0.893
≥30	18	3 (16.7%)	1.37	0.25–5.06	0.622	0.86	0.17–4.49	0.863
Sex								
Male	635	97 (15.3%)	Ref.					
Female	908	146 (16.1%)	1.06	0.80–1.42	0.670			
Health insurance schemes								
Civil servant medical benefit scheme	205	37 (18.0%)	1.28	0.83–1.92	0.225			
Social security scheme	151	21 (13.9%)	0.94	0.54–1.55	0.794			
Universal health coverage scheme	1040	153 (14.7%)	Ref.					
Others	140	31 (22.1%)	1.65	1.03–2.58	0.023*			
Education level								
Currently studying	887	132 (14.9%)	Ref.			Ref.		
Less than bachelor's degree	233	27 (11.6%)	0.75	0.46–1.18	0.200	0.63	0.33–1.20	0.161
Bachelor's degree, master's degree or higher	213	48 (22.5%)	1.66	1.12–2.44	0.007*	1.27	0.63–2.55	0.499
Insulin regimen and frequency of SMBG								
Conventional and ≤1 time/day	274	32 (11.7%)	Ref.			Ref.		
Conventional and 2 times/day	139	23 (16.6%)	1.50	0.80–2.78	0.169	1.89	0.99–3.60	0.053
Conventional and ≥3 times/day	148	18 (12.2%)	1.05	0.53–2.01	0.883	1.39	0.69–2.80	0.352
Intensive and ≤1 time/day	232	29 (12.5%)	1.08	0.61–1.91	0.777	1.05	0.57–1.96	0.867
Intensive and 2 times/day	161	18 (11.2%)	0.95	0.48–1.82	0.875	0.99	0.50–1.93	0.972
Intensive and ≥3 times/day	430	101 (23.5%)	2.32	1.49–3.69	<0.001*	2.80	1.71–4.58	<0.001*

Categorical data are presented as number and percentage. *A *P*-value <0.05 shows statistical significance. †Input variables were age, duration of disease, health insurance schemes, educational level, insulin regimen and self-monitoring of blood glucose (SMBG). AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; Ref., reference

duration of diabetes) among individuals with type 1 diabetes in Thailand. Consistent with the reports from Western countries[11–13], we found poor glycemic control to be common during adolescence and early adulthood, with subsequent gradual improvement in individuals aged >25 years. We also found a higher frequency of SMBG to be significantly associated with better glycemic control, as established by other studies[14–16]. Interestingly, just 0.69% of the present patients were aged ≥65 years. Although studies have shown that type 1 diabetes patients had a shorter life expectancy[17,18], it is unclear if this is responsible for the low detection rate in this age group in the current study. Lower awareness of type 1 diabetes in older adults among healthcare providers could partially explain this finding.

Importantly, the results of the present study clearly show that most patients with type 1 diabetes in Thailand have not achieved optimal glycemic control. Alarmingly, the mean HbA_{1c} and the percentage of patients that met the glycemic target in the current study (9.35 ± 2.41% and 16%, respectively) are not different from those reported from the Thailand Diabetes Registry Project, which was carried out in 2003 (a mean HbA_{1c} of 9.3 ± 2.5% in 195 children and adolescents, and 17% met glycemic target)[8]. Similarly, a previous study from Asia and the Western Pacific region that included 159 Thai children and adolescents during 2001–2002 found a mean HbA_{1c} of 9.0 ± 2.3%, 89.3% of them were receiving one or two injections daily, 10.7% were receiving three injections daily and none were receiving four injections daily or CSII[19]. Although the

proportion of patients using IIT in this cohort (57%) was significantly higher than a decade ago, their HbA_{1c} was still high at 9.17%, and just 18.6% achieved glycemic target. The present T1DDAR CN project clearly shows the worrisome fact that there has been no improvement in glycemic control in our type 1 diabetes patients during the past decade.

When comparing glycemic control between the present cohort and individuals with type 1 diabetes from developed countries[9,11,13,20,21], the present patients had a higher HbA_{1c} and a lower proportion of individuals achieving targeted glycemic control. Among these countries, Sweden had the lowest HbA_{1c} (7.6%) and the highest percentage of patients who achieved optimal glycemic control (49%)[20]. Sweden has a well-established national program that helps participating centers to improve their care for children with diabetes, along with a national quality registry (SWEDIABKIDS) that provides open online data that each center can access their performance and compare with other centers' as well as nationally[22]. Germany, and Austria had the next lowest mean HbA_{1c} (7.7–7.8%)[20]. In contrast, Australia, the UK, the USA and Wales showed higher HbA_{1c} levels (8.3–8.8%), and just 17–27% of patients had optimal glycemic control[9,20]. Similar to the findings from the Type 1 Diabetes Exchange clinic registry[11], the present patients aged >25 years had better glycemic control than our younger patients. However, just 15–18% of the patients met the targeted glycemic control, and their average HbA_{1c} was 8.03–8.85%, which is higher than the reported 7.6–7.7% from the Type 1 Diabetes Exchange[11].

The present cohort also showed patterns of insulin delivery in Thailand. Similar to findings from the Australasian Diabetes Data Network registry[9], CIT was commonly used in younger children, with 50–60% of Thai children aged <10 years using CIT. In Thailand, multiple daily injections are mainly prescribed for children who are aged >10 years who are deemed able to carry out insulin injections, or for those who have caregivers that can give insulin injection(s) during school hours. The fact that CIT is commonly prescribed for young school-aged children in Thailand might suggest that parents or school personnel have difficulty giving insulin injections or providing support for IIT. Another possible explanation might be the lack of a type 1 diabetes-specialized healthcare team to provide support for school personnel. Only 1% of our patients were on CSII. The high cost of CSII and the low number of experienced medical teams can explain the very low percentage of CSII use in Thailand.

The results from the T1DDAR CN study have illuminated the current status of type 1 diabetes care in Thailand. Despite more than half of patients being on IIT, the majority did not achieve optimal glycemic control. This can be explained by several factors. First, just 20% of the present patients carried out SMBG four or more times per day. The cost of the glucose test strips, currently not covered by any insurance, might partly explain the infrequency of SMBG. A study from Korea emphasized the necessity of a national reimbursement policy for blood glucose test strips[23]. The Korea National Health Insurance Service has reimbursed the cost of blood glucose test strips for up to four times a day for patients with type 1 diabetes since 2011. A study among 466 Korean patients with type 1 diabetes showed an increased proportion of patients who carried out SMBG four or more times per day after registering for a national reimbursement program: 28.4% at baseline and 44.1% at 12 month follow up[23]. Furthermore, an increase in SMBG frequency was associated with >5% reduction of HbA_{1c} at 12-month follow up[23]. Socioeconomic status has been reported to be associated with glycemic control[12]. More than half of our cohort had a monthly household income <$600, which is below the $840 average national income[24]. In addition to adversely affecting the adequacy of basic diabetes needs (e.g., glucose test strips, types and quality of meals etc.), low socioeconomic status might also affect the state of care and supervision in the home. The IDREAM study in India found parental involvement in insulin administration to be associated with better glycemic control[25]. Suboptimal glycemic control in our cohort might also be due to the omission of pre-main meal insulin injection or an extra injection for snack, especially in patients receiving multiple daily injections. Other possible factors include lack of the routine use of flexible insulin dosing coupled with carbohydrate counting. We then arrive at the important question – what is the availability and effectiveness of the DSMES provided among hospitals in Thailand. A recent nationwide survey showed that 30% of diabetes educators in Thailand reported that the diabetes education in their hospitals was successful, whereas 37–43% reported uncertainty regarding the program's effectiveness, and 24–32% said that the program's effectiveness was not evaluated[26]. One of the obstacles reported was lack of time for diabetes educators to provide education due to their need to attend to other duties[26]. The uncertainty of the effectiveness and lack of formal evaluation of diabetes education are weak points in the process of diabetes care in Thailand[26]. Finally, psychological factors might influence glycemic control. The burden and the demands of having type 1 diabetes in managing daily diabetes-related tasks can lead to negative emotions or "diabetes distress"[27] and depressive symptoms[28,29]. Depressive symptoms are common in adolescents with type 1 diabetes, and have been shown to be related to decreased self-care and poor glycemic control[28,29].

The Thailand Diabetes Registry Project in 2003 reported a prevalence of diabetic retinopathy and diabetic nephropathy of 21.6 and 44.4%, respectively in type 1 diabetes patients[30,31]. Although the overall prevalence of diabetic retinopathy and nephropathy was lower in the current study than the previous study, the prevalence of both complications increased dramatically in older patients. It is also of great concern that diabetic nephropathy had already developed in our young cohort. We found that patients who were treated with IIT had a lower prevalence of diabetic retinopathy, which supports the reported benefit of IIT on microvascular complications[32]. The overall prevalence of diabetic neuropathy in our cohort was 5.2%,

which is quite similar to the prevalence of 7% in the SEARCH for Diabetes in Youth study[33]. However, only one-third of our patients had the neuropathy assessment, suggesting that improvement in care process is required.

Patterns of acute complications (hypoglycemia and DKA) in the current study are also worrisome. Previously, data from Asia and the Western Pacific Region in 2001–2002 showed an incidence of hypoglycemia events in Thailand of 75.9 events per 100 patient-years, and the incidence of DKA events was 11.4 per 100 patient-years[19]. The incidence of hypoglycemia among Thai children was similar to that of the region (74 events per 100 patient-years); however, the incidence of DKA was modestly higher (region – 9.9 events per 100 patient-years)[19]. The prevalence of severe hypoglycemia in the T1DDAR CN project was 8.5% per year, and the prevalence was highest in participants aged ≥45 years. The present finding is similar to that reported from the Type 1 Diabetes Exchange registry, which found that 6% of participants had severe hypoglycemia within the previous 3 months, and that the rate increased in older patients[11]. However, the present cohort had a considerably higher prevalence of DKA (10.2% per year) than that of the Type 1 Diabetes Exchange registry (3% of participants reported having a DKA event within the previous 3 months)[11]. This observed high rate of DKA can partly be explained by poor glycemic control and the fact that most participating hospitals did not have a system in place to assist patients with impending DKA (e.g., no 24-h telephone consultation service). The present results showed no difference in the prevalence of DKA and severe hypoglycemia between CIT and IIT groups.

The present study had some limitations. First, this study recruited only patients from tertiary centers, so these results might not be generalizable for the entire country. Second, this study did not evaluate other factors that might influence glycemic control, such as psychological status and self-care behaviors. Finally, HbA_{1c} was assayed at each tertiary hospital and not at one centralized laboratory.

In conclusion, the T1DDAR CN study comprises the largest national cohort of type 1 diabetes patients to date in Thailand. The results of this important study showed that most patients do not meet the recommended glycemic target, facing a high risk of complications. Further study is required to prioritize the factors that will influence improvement in glycemic control. Changes to Thailand's national health policy in type 1 diabetes care, including the provision of optimal glucose test strips and glucometer, establishing a referral system to experienced diabetologists, and the development and implementation of a standardized DSMES system at the national level, are urgently required. As the results of the present study, a national program to improve the quality of diabetes treatment and DSMES has been implemented since October 2018, and the result is ongoing.

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DISCLOSURE

The authors declare no conflict of interest.

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APPENDIX 1

The following persons participated in the T1DDAR CN:

Central region

University Hospitals: King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok (Taninee Sahakitrungruang, Suphab Aroonparkmongkol, Vichit Supornsilchai); Ramathibodi Hospital, Mahidol University, Bangkok (Chardpraorn Ngarmukos, Hataikarn Nimitphong, Manassawee Korwutthikulrangsri, Patcharin Khlairit, Pat Mahachoklertwattana, Preamrudee Poomthavorn, Ratanaporn Jerawatana, Sarunyu

Pongratanakul, Sirimon Reutrakul); Siriraj Hospital, Mahidol University, Bangkok (Apiradee Sriwijitkamol, Jeerunda Santiprabhob, Lukana Preechasuk, Ornsuda Lertbannaphong, Raweewan Lertwattanarak, Sriwan Thongpaeng, Supawadee Likitmaskul, Supitcha Patjamontri); Thammasat University Hospital, Pathum Thani (Nattamon Tanathornkirati, Pitvara Panpitpat, Pontipa Engkakul, Thipaporn Tharavanij); Vajira Hospital, Navamindradhiraj University, Bangkok (Natphassorn Dermkhuntod, Petch Rawdaree, Thanyaros Sinsophonphap, Warunee Sunpakaew).

Hospitals in the Ministry of Public Health: Charoenkrung Pracharak Hospital, Bangkok (Phatharaporn Kiatpanabhikul, Supawut Suksantilirs); Queen Sirikit National Institute of Child Health, Bangkok (Chawkaew Kongkanka, Nutlita Boonkong, Sirinya Somsaen); Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok (Apatsara Vansaksri, Chaicharn Deerochanawong); Sawanpracharak Hospital, Nakhon Sawan (Chattama Chairat, Kamonwan Chanchalam, Sanguansak Siangruangsang); Taksin Hospital, Bangkok (Worraporn Tantichattanon).

Hospitals in the Ministry of Defense: Bhumibol Adulyadej Hospital, Bangkok (Chulalak Nganlasome, Karnsuda Pichetsin, Kesinee Boonpakdee)

HRH Princess Maha Chakri Sirindhorn Medical Center-MSMC Hospital, Nakhon Nayok (Nattakarn Wongjitrat); Phramongkutklao Hospital, Bangkok (Jiraporn Nuphonthong, Nattapol Sathavarodom, Nawaporn Numbenjapon); Somdejprapinklao Hospital, Bangkok (Chantraporn Keamseng).

North region

University Hospitals: Chiang Mai University Hospital, Chiang Mai (Danil Wongsa, Laddawan Limpijankit, Mattabhorn Phimphilai, Prapai Dejkhamron).

Hospitals in the Ministry of Public Health: Buddhachinaraj Hospital, Phitsanulok (Meijinee Densriwiwat); Chiangrai Prachanukroh Hospital, Chiang Rai City (Kiran Sony, Orathai Mahawongsanan, Pataree Maneerat); Nakornping Hospital, Chiang Mai (Hataitip Tangngam, Tattiwa Nirach).

Northeast region

University Hospitals: Srinagarind Hospital, Khon Kaen University, Khon Kaen (Chatlert Pongchaiyakul, Ouyporn Panamonta, Pattara Wiromrat).

Hospitals in the Ministry of Public Health: Khon Kaen Hospital, Khon Kaen (Chatchai Suesirisawad); Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima (Priya Sanguanwongwichit, Puntip Tantiwong, Sirilak Setthalak); Mukdahan Hospital, Mukdahan (Akanit Jindamaneemas, Nattakarn Suwansaksri); Sunpasitthiprasong Hospital, Ubon Ratchathani (Jaturat Petchkul).

East region

University Hospitals: Burapha University Hospital, Chonburi (Krittha Jeerawongpanich).

Hospitals in the Ministry of Public Health: Chonburi Hospital (Somlak Tongmeesee); Prapokklao Hospital, Chanthaburi (Thapana Roonghiranwat); Rayong Hospital, Rayong (Chotima Sornsiriwong, Naruewan Piriyabanjong, Tippawan Kongvitayanon).

South region

University Hospitals: Songklanagarind Hospital, Prince of Songkla University, Songkhla (Rattana Leelawattana, Somchit Jaruratanasirikul).

Hospitals in the Ministry of Public Health: Hat Yai Hospital, Songkhla (Pathikan Dissaneevate); Maharaj Nakhon Si Thammarat Hospital, Nakhon Si Thammarat (Saowanee Nakkaew); Surat Thani Hospital, Surat Thani (Palinee Nantarakchaikul).