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ORIGINAL ARTICLE

Young-onset diabetes patients in Thailand: Data from Thai Type 1 Diabetes and Diabetes diagnosed Age before 30 years Registry, Care and Network (T1DDAR CN)

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Keywords
Patients, Thai Type 1 Diabetes and Diabetes diagnosed Age before 30 years Registry, Care and Network, Young-onset diabetes

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ABSTRACT

Aims/Introduction: There is a lack of current information regarding young-onset diabetes in Thailand. Thus, the objectives of this study were to describe the types of diabetes, the clinical characteristics, the treatment regimens and achievement of glycemic control in Thai patients with young-onset diabetes.

Materials and Methods: Data of 2,844 patients with diabetes onset before 30 years-of-age were retrospectively reviewed from a diabetes registry comprising 31 hospitals in Thailand. Gestational diabetes was excluded.

Results: Based on clinical criteria, type 1 diabetes was identified in 62.6% of patients, type 2 diabetes in 30.7%, neonatal diabetes in 0.8%, other monogenic diabetes in 1.7%, secondary diabetes in 3.0%, genetic syndromes associated with diabetes in 0.9% and other types of diabetes in 0.4%. Type 1 diabetes accounted for 72.3% of patients with age of onset <20 years. The proportion of type 2 diabetes was 61.0% of patients with age of onset from 20 to <30 years. Intensive insulin treatment was prescribed to 55.2% of type 1 diabetes patients. Oral antidiabetic agent alone was used in 50.8% of type 2 diabetes patients, whereas 44.1% received insulin treatment. Most monogenic diabetes, secondary diabetes and genetic syndromes associated with diabetes required insulin treatment. Achievement of glycemic control was identified in 12.4% of type 1 diabetes patients, 30% of type 2 diabetes patients, 36.4% of neonatal diabetes patients, 28.3% of other monogenic diabetes patients,

†The members of T1DDAR CN group are listed in Appendix 1.

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45.6% of secondary diabetes patients and 28% of genetic syndromes associated with diabetes patients.

Conclusion: In this registry, type 1 diabetes remains the most common type and the prevalence of type 2 diabetes increases with age. The majority of patients did not achieve the glycemic target, especially type 1 diabetes patients.

INTRODUCTION

Diabetes causes burden individually and nationally, especially if diabetes-related complications develop. Globally, the incidence of type 1 diabetes has been increasing[1], and a similar trend in type 2 diabetes in children and adolescents has been observed that has accompanied the rise in adolescent obesity[2]. Thailand is also facing an increase in the numbers of patients with diabetes[3]. The incidence rate has increased from 0.15/100,000/year in 1984–1985[4] to 1.65/100,000/year in 1991–1995[5]. An increased prevalence of type 2 diabetes in Thai children and adolescents associated with the rising prevalence of obesity has also been observed[6]. However, there is a lack of current information regarding the types, clinical characteristics and achievement of glycemic control of young-onset diabetes in Thailand.

The Thai Type 1 Diabetes (all ages) and Diabetes diagnosed Age before 30 years Registry, Care and Network (T1DDAR CN), which is a collaboration among the Diabetes Association of Thailand, the Thai Society for Pediatric Endocrinology, the Endocrine Society of Thailand, the National Health Security Office of Thailand, the Siriraj Diabetes Center of the Faculty of Medicine Siriraj Hospital, Mahidol University and the Northern Diabetes Center of the Faculty of Medicine, Chiang Mai University, was established in 2014[7]. The goals of T1DDAR CN were to build a diabetes registry to enhance the network of diabetes care and improve diabetes self-management education and support, which had not previously been standardized in Thailand. The T1DDAR CN strategy has been implemented at and through 31 regional collaborating government tertiary care hospitals (see Appendix 1)[7].

The objectives of the present study were to characterize the types of diabetes among Thai patients with diabetes diagnosed before age of 30 years, including clinical characteristics, year of diagnosis, treatment regimens and glycemic control. This information will provide healthcare professionals and government policymakers with crucial perspectives specific to the quality of diabetes care among young-onset patients in Thailand.

MATERIALS AND METHODS

The present retrospective study was carried out among 31 T1DDAR CN network hospitals during July 2016 to July 2017. Patients' inclusion criteria were age at diagnosis of diabetes <30 years and current attendance of clinics at each collaborating hospital. Patients with gestational diabetes were excluded. An electronic case record form was developed using the web-based program Research Electronic Data Capture (Vanderbilt University, Nashville, TN, USA). Details specific to electronic data management were published elsewhere[7].

Patient data, including the type of diabetes, patient characteristics, age of onset, year of diagnosis, number of new cases each year, presentation of diabetic ketoacidosis (DKA) or diabetes symptoms at diagnosis, diabetes autoantibodies, latest glycated hemoglobin (HbA_{1c}) value, daily self-monitoring of blood glucose (SMBG) and treatment, were reviewed. Insulin regimen was defined as conventional insulin treatment (insulin 1–3 injections/day) or intensive insulin therapy (multiple daily injections ≥4 injections/day or continuous subcutaneous insulin infusion). Comorbidities, including autoimmune thyroiditis, dyslipidemia and hypertension, were also recorded. Dyslipidemia was diagnosed if the low-density lipoprotein cholesterol (LDL-C) level was >100 mg/dL, or if patients were on hyperlipidemia treatment. Hypertension was diagnosed if patients had elevated blood pressure or were treated with antihypertensive medication[7]. Glycemic control was classified as: (i) good glycemic control: HbA_{1c} <7.0%; (ii) fair glycemic control: HbA_{1c} within the range of 7.0–9.0%; and (iii) poor glycemic control: HbA_{1c} >9%. The present study did not include diabetic complications in the results, as they were published elsewhere[7].

The study protocol was approved by the Central Research Ethics Committee of Thailand (approval number CREC 009/2559BRm), and by the institutional review board of each participating center.

Case definitions

Types of diabetes were classified based on the clinical assessment by pediatric or adult endocrinologists at each participating center. The clinical diagnoses were reviewed and agreed on by the T1DDAR CN investigators. Clinical characteristics, glycemic control and treatment regimens were analyzed based on the type of diabetes according to the World Health Organization 2019 classifications[8] with some modifications. Due to the unavailability of diabetes autoantibodies measurement in the majority of patients, hybrid form of diabetes was not included. Other specific types of diabetes; that is, drug-induced diabetes, disorder of the pancreas, infection-induced diabetes and endocrinopathy-related diabetes, were defined as secondary diabetes. The definitions of different types of diabetes are as follows:

Type 1 diabetes

Type 1 diabetes is characterized by β-cell destruction (mostly immune-mediated) and absolute insulin deficiency. Patients

who presented with acute symptoms, marked hyperglycemia with or without ketoacidosis and required insulin therapy within the first year after diagnosis, with or without the presence of diabetes autoantibodies, were considered as having type 1 diabetes.

Type 2 diabetes

Type 2 diabetes is characterized by various degrees of β-cell dysfunction and insulin resistance. Patients who presented with signs of insulin resistance or had preserved insulin secretion, not requiring insulin therapy to control hyperglycemia within the first year of diagnosis, were diagnosed with type 2 diabetes.

Monogenic diabetes

Diagnosis of monogenic diabetes was made if patients had monogenic defects of β-cell functions, such as neonatal diabetes, maturity onset diabetes of the young (MODY), mitochondrial diabetes, Wolfram syndrome or monogenic defects in insulin action (Rabson–Mendenhall syndrome)[8]. Neonatal diabetes was considered in patients who presented with symptoms of diabetes or who were diagnosed with diabetes within the first 6 months of life. MODY was diagnosed in patients with a family history of diabetes diagnosed before the age of 25 years in at least three consecutive generations with the autosomal dominant pattern. Mitochondrial diabetes was considered in patients with maternally-inherited diabetes with multi-organ involvement, such as encephalopathy, myopathy, sensorineural deafness and pigmentary retinal dystrophy[9]. Wolfram syndrome was diagnosed in patients with childhood-onset diabetes mellitus, optic nerve atrophy, hearing loss, diabetes insipidus and neurodegeneration[10]. Rabson–Mendenhall syndrome was diagnosed in patients with insulin-resistant diabetes with multiple features, including coarse faces, lichenified skin, acanthosis nigricans, fasting hypoglycemia, postprandial hyperglycemia, pineal hyperplasia and growth retardation[11]. In the present study, neonatal diabetes was analyzed separately, whereas patients with MODY and other monogenic diabetes were grouped and analyzed as other monogenic diabetes. Genetic testing was carried out in-house at each center or sent out to an available laboratory.

Secondary diabetes

Secondary diabetes was considered if patients had a diagnosis of drug-induced diabetes, disorder of the pancreas, infection-induced diabetes or endocrinopathy-related diabetes.

Genetic syndrome associated with diabetes

This diagnosis was considered in patients having Prader–Willi syndrome, Down syndrome, Turner syndrome and others.

Other types of diabetes

Patients were classified in this type if the diagnosis was uncertain or not consistent with the criteria for any of the aforementioned diabetes diagnoses.

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 they were included in other analyses for which data were available. Data are presented as the number and percentage for categorical data, and as mean plus/minus standard deviation for continuous data.

RESULTS

Types of diabetes and numbers of cases diagnosed per year

A total of 2,844 cases of diabetes diagnosed before 30 years-of-age were analyzed. The diagnoses by clinical criteria were patients with type 1 diabetes 62.6%, type 2 diabetes 30.7%, monogenic diabetes 2.5%, secondary diabetes 3.0%, genetic syndromes associated with diabetes 0.9% and other types of diabetes 0.4% (Table 1). Among the 71 patients with monogenic diabetes, 35 had MODY, 23 neonatal diabetes, eight Wolfram syndrome, three mitochondrial diabetes and one Rabson–Mendenhall syndrome. Secondary diabetes was observed in 84 patients (Table 2). Drug-induced diabetes and disorders of the pancreas were common causes of secondary diabetes. Genetic syndromes associated with diabetes were found in 25 patients, including 13 Prader–Willi syndrome, eight Down syndrome, two Turner syndrome, one Peters-plus syndrome and one mental retardation. When considering the year of diagnosis, we observed a higher number of patients diagnosed with diabetes in recent years compared with earlier years (Figure 1a). Type 1 diabetes was the most common type of diabetes in patients with age of onset 0 to <15 years throughout 1976–2016, and in patients with age of onset 15 to <30 years during 1981–1990 and 1996–2000. An increased percentage of type 2 diabetes in the 0 to <15 age group during 1996–2016 was also observed. Type 2 diabetes was the most common type of diabetes in patients with age of onset 15 to <30 years during 1991–1995, and during 2006–2016 (Figure 1b,c).

Patient characteristics

Females were predominant in all types of diabetes. The overall mean duration of diabetes was 7.1 ± 6.0 years. The mean age at diagnosis in type 1 diabetes patients was 12.2 ± 6.8 years, and the youngest case was diagnosed at the age of 10 months. Type 2 diabetes patients had the highest average age of onset (20.8 ± 6.2 years), with the youngest patient diagnosed at 7.8 years (Table 1). Type 1 diabetes accounted for 72.3% of patients, with age of onset <20 years (Figure 2). The number of cases diagnosed with type 1 diabetes peaked at 10 to <15 years-of-age, followed by 5 to <10 years-of-age. The proportion of type 2 diabetes increased substantially with age. The proportion of type 2 diabetes was 61.0% of patients with age of onset from 20 to <30 years. Among all types of diabetes, most cases of diabetes were diagnosed between 10 and <15 years-of-age (Figure 2).

Table 1 | Demographic and clinical characteristics, comorbidities, glycemic control, and frequency of self-monitoring of blood glucose among 2,844 diabetes patients diagnosed before age 30 years

	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes		Secondary diabetes	Genetic syndromes associated with diabetes	Other
			Neonatal diabetes	Other monogenic diabetes			
n (%)	1,782 (62.6%)	872 (30.7%)	23 (0.8%)	48 (1.7%)	84 (3.0%)	25 (0.9%)	10 (0.4%)
Age at diagnosis, years (mean ± SD)	12.2 ± 6.8	20.8 ± 6.2	0.2 ± 0.2	13.6 ± 7.4	14.4 ± 7.1	12.6 ± 6.1	15.7 ± 8.7
(range)	(0.8–29.9)	(7.8–29.9)	(0–0.9)	(1.0–29.8)	(0–28.4)	(0.9–25.7)	(2.0–26.4)
Age at registry entry, years (mean ± SD)	19.3 ± 9.1	26.2 ± 8.7	9.2 ± 6.4	22.3 ± 7.7	19.7 ± 8.3	19.5 ± 6.0	24.1 ± 11.6
Female sex, *n* (%)	1,059 (59.4%)	525 (60.2%)	12 (52.2%)	38 (79.2%)	47 (56.0%)	14 (56.0%)	6 (60.0%)
Duration of disease, years (mean ± SD)	7.6 ± 6.3	5.9 ± 5.1	9.4 ± 6.3	9.2 ± 6.4	5.3 ± 5.1	7.5 ± 5.7	8.4 ± 7.3
DKA at diagnosis							
Available records (*n*)	1,476	667	20	42	79	22	7
Presence of DKA at diagnosis, *n* (%)	1,000 (67.8%)	80 (12.0%)	13 (65.0%)	6 (14.3%)	16 (20.2%)	8 (36.4%)	1 (14.3%)
Diabetes symptoms at diagnosis							
Available records (*n*)	448	552	7	33	60	14	5
Presence of diabetes symptoms at diagnosis, *n* (%)	383 (85.5%)	297 (53.8%)	2 (28.6%)	22 (66.7%)	27 (45.0%)	4 (28.6%)	2 (40.0%)
Diabetes antibodies performed (*n*)	686	155	9	28	21	3	4
Negative, *n* (%)	186 (27.1%)	151 (97.4%)	9 (100%)	28 (100%)	21 (100%)	2 (66.7%)	4 (100%)
Positive, *n* (%)	500 (72.9%)	4 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Autoimmune thyroid disease							
Available records, *n*	1,782	872	23	48	63	25	6
Presence of autoimmune thyroid disease, *n* (%)	85 (4.8%)	10 (1.2%)	0 (0.0%)	0 (0.0%)	2 (2.4%)	3 (12.0%)	0 (0.0%)
Dyslipidemia							
Available records (*n*)	1,782	872	23	48	84	25	10
Presence of dyslipidemia, *n* (%)	460 (25.8%)	486 (55.7%)	1 (4.4%)	19 (39.6%)	20 (23.8%)	12 (48.0%)	3 (30.0%)
Hypertension							
Available records (*n*)	1,782	872	23	48	84	25	10
Presence of hypertension, *n* (%)	147 (8.2%)	290 (33.3%)	0 (0.0%)	6 (12.5%)	15 (17.9%)	6 (24.0%)	2 (20.0%)
HbA_{1c}, % (mean ± SD)	9.41 ± 2.43	8.48 ± 2.40	7.64 ± 1.87	9.38 ± 3.37	7.78 ± 2.29	8.82 ± 2.63	8.72 ± 2.65
SMBG frequency							
Available records, *n*	1,594	714	20	43	73	22	7
Mean SMBG (times/day)	2.1 ± 1.4	0.4 ± 0.8	2.1 ± 1.5	1.3 ± 1.2	0.9 ± 1.0	1.0 ± 1.1	1.7 ± 1.7
Not performed, *n* (%)	269 (16.9%)	495 (69.3%)	3 (15.0%)	13 (30.2%)	33 (45.2%)	9 (40.9%)	3 (42.9%)
≤1/day, *n* (%)	349 (21.9%)	153 (21.4%)	6 (30.0%)	14 (32.6%)	19 (26.0%)	5 (22.7%)	0 (0.0%)
2/day, *n* (%)	333 (20.9%)	41 (5.7%)	3 (15.0%)	10 (23.3%)	19 (26.0%)	7 (31.8%)	1 (14.3%)
3/day, *n* (%)	322 (20.2%)	18 (2.5%)	2 (10.0%)	4 (9.3%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
≥4/day (%)	321 (20.1%)	7 (1.0%)	6 (30.0%)	2 (4.6%)	2 (2.7%)	1 (4.6%)	1 (14.3%)

DKA, diabetic ketoacidosis; HbA_{1c}, glycated hemoglobin; SD, standard deviation; SMBG, self-monitoring of blood glucose

Table 2 | Causes of secondary diabetes in this study

Causes	*n* (%)
Drug-induced diabetes	41 (48.8%)
Glucocorticoid	32 (38.1%)
L-asparaginase	6 (7.1%)
Tacrolimus	2 (2.4%)
Antiretroviral drug	1 (1.2%)
Disorder of pancreas	39 (46.4%)
Post-pancreatectomy	17 (20.2%)
Pancreatic hemochromatosis	11 (13.1%)
Pancreatitis and others	11 (13.1%)
Infection-induced diabetes	2 (2.4%)
Cytomegalovirus	2 (2.4%)
Endocrinopathy	2 (2.4%)
Growth hormone-producing pituitary adenoma	2 (2.4%)

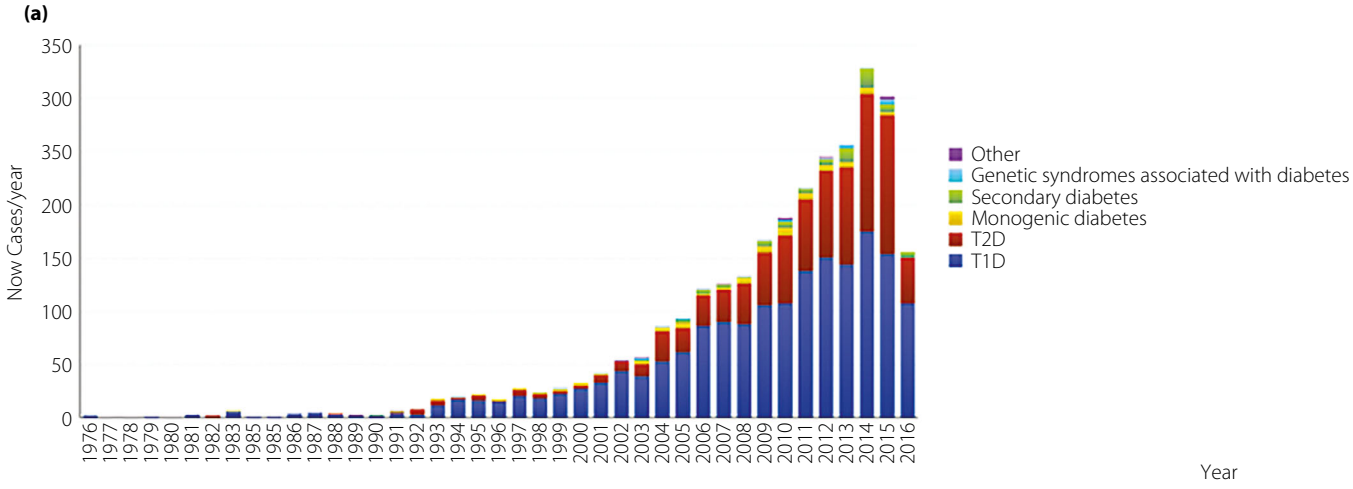
Total *n* = 84.

Presentation at diagnosis

Presentation with DKA was most common in type 1 diabetes patients (67.8%), followed by 65.0% in neonatal diabetes patients. In contrast, just 12.0% of type 2 diabetes patients presented with DKA. Over three-quarters (85.5%) of type 1 diabetes patients, 54% of type 2 diabetes and 67% of other monogenic diabetes had diabetes symptoms at diagnosis (Table 1).

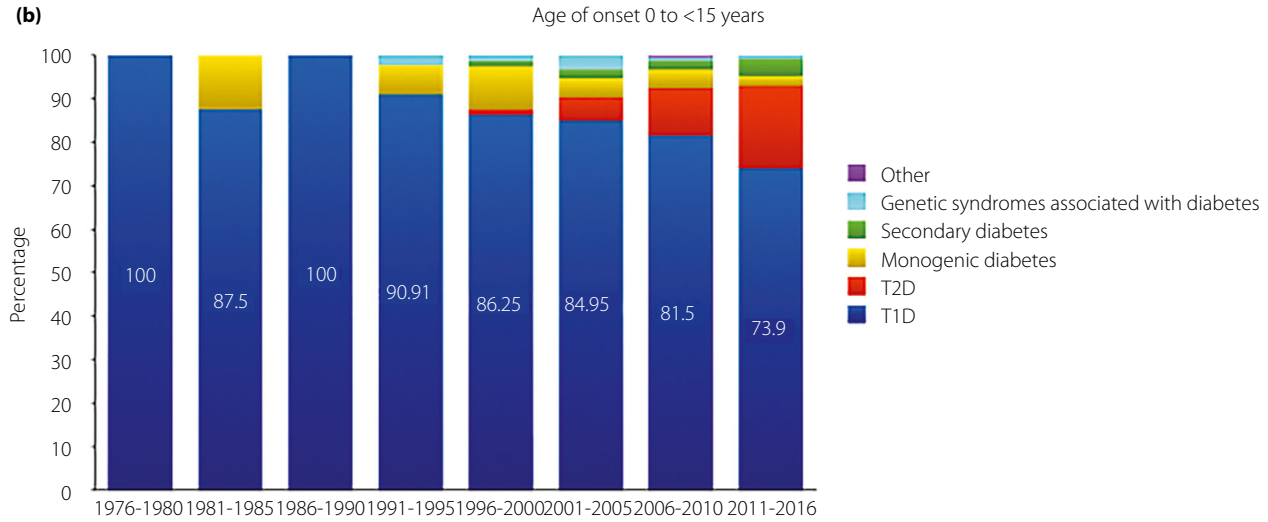
Diabetes autoantibodies

Diabetes autoantibodies testing was carried out in 31.9% of patients. Among the 686 type 1 diabetes patients who had a diabetes autoantibodies test carried out, 72.9% tested positive for one or more of the autoantibodies (Table 1). The majority (97.4%) of type 2 diabetes patients who were tested had a negative autoantibodies result. A low 2.6% had detectable levels, but the diagnosis of type 2 diabetes was made based on the clinical



Years	Average cases diagnosed per year					
	T1D	T2D	Monogenic diabetes	Secondary diabetes	Genetic syndromes associated with diabetes	Other
1976-1980	1.50	0	0	0	0	0
1981-1985	2.20	0.40	0.20	0	0	0
1986-1990	3.20	0.40	0	0.20	0	0
1991-1995	10.20	3.60	0.60	0.20	0.20	0.20
1996-2000	20.40	3.40	1.60	0.40	0.20	0
2001-2005	46.20	15.40	2.60	0.80	1.20	0.40
2006-2010	95.40	42.0	4.20	3.80	1.0	0.60
2011-2016	144.83	90.17	4.17	9.0	2.0	0.67

Figure 1 | (a) Number of diabetes patients according to the year of diagnosis during 1976–2016. (b) Percentage of different types of diabetes in patients with age of onset 0 to <15 years during 1976–2016. (c) Percentage of different types of diabetes in patients with age of onset 15 to <30 years during 1976–2016. T1D, type 1 diabetes; T2D, type 2 diabetes.



Years	Percentage of patients with different types of diabetes					
	T1D	T2D	Monogenic diabetes	Secondary diabetes	Genetic syndromes associated with diabetes	Other
1976-1980	100.0	0	0	0	0	0
1981-1985	87.50	0	12.50	0	0	0
1986-1990	100.0	0	0	0	0	0
1991-1995	90.91	0	6.82	0	2.27	0
1996-2000	86.25	1.25	10.0	1.25	1.25	0
2001-2005	84.95	5.38	4.30	2.15	3.23	0
2006-2010	81.50	11.01	4.22	2.11	0.70	0.47
2011-2016	73.90	19.19	2.15	3.81	0.72	0.24

Figure 1 | (b) Continued

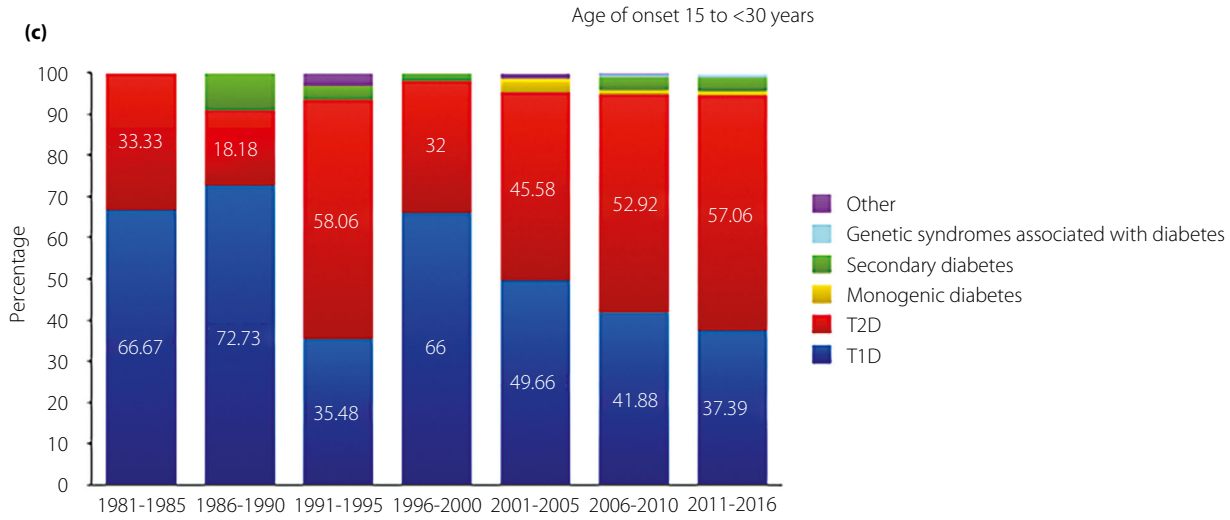
course of insulin independence. These patients maintained euglycemia with oral antidiabetic agents. One patient with Down syndrome had positive diabetes autoantibodies and was treated with conventional insulin regimen.

Genetic testing in monogenic diabetes

Genetic testing was not carried out in most patients diagnosed with monogenic diabetes. Most of those diagnoses were based solely on clinical manifestation. The diagnosis was confirmed by genetic testing in five patients with neonatal diabetes (two patients with KCNJ11 gene mutation – one had transient neonatal diabetes and one had intermediate DEND syndrome (developmental delay and neonatal diabetes); two patients had *INS* gene mutation; and one had chromosome 6q24-related diabetes). Among the patients diagnosed with MODY, genetic testing was carried out in just two patients. However, there was no mutation identified in these patients. A diagnosis of MODY-X was made in these patients based on their clinical profiles.

Treatment regimens

Among type 1 diabetes patients, 44.8% received conventional insulin treatment, and 55.2% received intensive insulin treatment. The following antidiabetic agents were prescribed in addition to insulin in 6.1% of type 1 diabetes patients: metformin 78.7%, thiazolidinedione 10.7%, sulfonylurea 4.9% and others 5.7%. A total of 50% of type 2 diabetes patients were treated with oral antidiabetic agent only, 32.5% of patients required oral antidiabetic agent and insulin therapy, and 5.1% required no medication. Metformin was the most commonly prescribed oral antidiabetic agent for type 2 diabetes patients (79.7%), followed by sulfonylurea (29.6%), thiazolidinedione (12.3%), acarbose (2.7%) and glinide (2.2%). More than half of patients with neonatal diabetes required insulin treatment. The majority of patients with monogenic diabetes, secondary diabetes, genetic syndrome associated with diabetes and other types of diabetes required insulin treatment with or without another antidiabetic agent. Patients with type 2 diabetes,



Years	Percentage of patients with different types of diabetes					
	T1D	T2D	Monogenic diabetes	Secondary diabetes	Genetic syndromes associated with diabetes	Other
1976-1980	0	0	0	0	0	0
1981-1985	66.67	33.33	0	0	0	0
1986-1990	72.73	18.18	0	9.09	0	0
1991-1995	35.48	58.06	0	3.23	0	3.23
1996-2000	66.0	32.0	0	2.0	0	0
2001-2005	49.66	45.58	3.40	0	0	1.36
2006-2010	41.88	52.92	0.97	3.25	0.65	0.32
2011-2016	37.39	57.06	1.05	3.30	0.90	0.30

Figure 1 | (c) Continued

secondary diabetes, genetic syndrome associated with diabetes and other types of diabetes who required insulin therapy were mainly on a conventional insulin regimen (Table 3).

Glycemic control

The average HbA_{1c} was highest in the type 1 diabetes patients (9.41 ± 2.43%), and lowest in the neonatal diabetes patients (7.64 ± 1.87%; Table 1). Good glycemic control was identified in 12.4% of type 1 diabetes patients compared with 30.0% of type 2 diabetes patients, 36.4% of neonatal diabetes patients, 28.3% of other monogenic diabetes patients, 45.6% of secondary diabetes patients, 28.0% of genetic syndrome associated with diabetes patient, and 33.3% of other types of diabetes patients. As a total cohort, just 19.4% of patients achieved HbA_{1c} targets (Figure 3).

SMBG

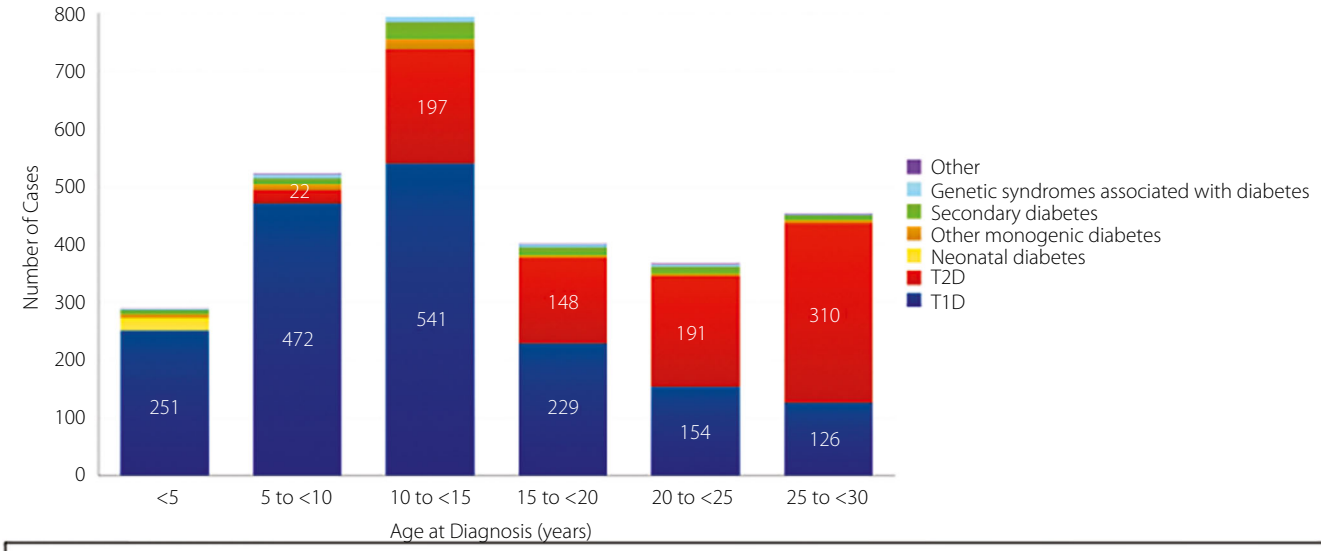
The frequency of daily SMBG among our cohort is shown in Table 1. The average number of SMBG in type 1 diabetes patients was 2.1 ± 1.4 times/day. Just 20.1% of type 1 diabetes patients carried out SMBG four or more times/day, and 16.9% did not carry out SMBG at all. The majority of type 2 diabetes patients did not carry out SMBG (Table 1).

Comorbidities

The prevalence of autoimmune thyroid disease was highest in genetic syndrome associated with diabetes patients (12%), followed by type 1 diabetes patients (4.8%). The prevalence of dyslipidemia and hypertension were highest in type 2 diabetes patients at 55.7% and 33.3%, respectively (Table 1).

DISCUSSION

The results of this nationwide multicenter registry hospital-based study of young-onset diabetes showed a recent increase in the number of patients diagnosed with diabetes, both type 1 diabetes and type 2 diabetes. The present finding is similar to the SEARCH Diabetes in Youth Study in the USA, which also showed the increased prevalence of both type 1 diabetes and



Age at Diagnosis (years)	Percentage of patients with different types of diabetes in each age group						
	T1D	T2D	Neonatal diabetes	Other monogenic diabates	Secondary diabetes	Genetic sysndromes associated with diabetes	Other
<5	86.55	0	7.93	1.72	2.76	0.69	0.34
5 to <10	90.25	4.21	0	1.91	2.10	1.15	0.38
10 to <15	68.05	24.78	0	2.26	3.65	1.13	0.13
15 to <20	56.97	36.82	0	1.00	3.73	1.0	0.50
20 to <25	41.96	52.04	0	1.36	3.27	0.82	0.54
25 to <30	27.75	68.28	0	1.32	1.98	0.22	0.44

Figure 2 | Distribution of different types of diabetes in each age group at diagnosis. T1D, type 1 diabetes; T2D, type 2 diabetes.

type 2 diabetes[12]. However, in the present study, the number of patients diagnosed in 2016 was lower than in previous years. We speculate that many patients were taken care of at community and/or general hospitals, and were not referred for care to tertiary care centers during the first year of diagnosis. In this study, type 1 diabetes was found to be more common in the first and the second decades of life, whereas type 2 diabetes was observed to be more common in the third decade of life. The increased number of type 1 diabetes cases diagnosed recently in our registry is similar to the increased incidence reported in the USA[13] and other countries[14]. However, in Finland, a country with a high incidence of type 1 diabetes, the incidence of type 1 diabetes increased during 1953–2006, but since 2006, that trend has been decreasing[15]. Several factors; for example, obesity (accelerator hypothesis), gut microbiome, exposure to several chemicals and early life factors, including maternal diet, mode of delivery, infant feeding, childhood diet and microbial exposure (hygiene hypothesis), might contribute to the increasing incidence of type 1 diabetes in certain populations[16]. The present study found that type 1 diabetes (62.6%) and type 2 diabetes (30.7%) accounted for the majority of cases with young-onset diabetes. This is consistent with a report from a registry of people with diabetes in India with young age at onset (YDR)[17], which showed a prevalence of type 1 diabetes of 63.9%, and a prevalence of type 2 diabetes of 25.3%[17]. In contrast, a study in Japan showed that 57.4% of patients with early-onset diabetes were found to have type 2 diabetes[18]. The higher proportion of type 1 diabetes in the present study might partly be explained by the possibility that not all patients with type 2 diabetes were referred to the tertiary care centers. Furthermore, the number of patients with type 2 diabetes might be underestimated, because some patients might be asymptomatic and did not seek diagnosis or treatment. Nevertheless, during recent years, an increased percentage of patients diagnosed with type 2 diabetes in both age of onset <15 years and within 15 to <30 years was observed in the present study. Obesity, living an obesogenic lifestyle[19] and possibly, an increase in surveillance for type 2 diabetes[20], might

Table 3 | Treatment regimen in 2,844 diabetes patients diagnosed before 30 years-of-age compared among different types of diabetes

	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes		Secondary diabetes	Genetic syndromes associated with diabetes	Other
			Neonatal diabetes	Other monogenic diabetes			
Treatment regimen (*n*)	1,778	870	23	48	84	25	10
1. Insulin only, *n* (%)	1,670 (93.9%)	101 (11.6%)	14 (60.9%)	15 (31.2%)	48 (57.1%)	8 (32.0%)	7 (70.0%)
2. Insulin and antidiabetic agent, *n* (%)	108 (6.1%)	283 (32.5%)	0 (0.0%)	22 (45.8%)	9 (10.7%)	10 (40.0%)	1 (10.0%)
Insulin regimen							
Conventional treatment, *n* (%)	786 (44.8%)	322 (84.5%)	10 (71.4%)	25 (67.6%)	39 (68.4%)	14 (77.8%)	6 (75.0%)
Intensive treatment, *n* (%)	968 (55.2%)	59 (15.5%)	4 (28.6%)	12 (32.4%)	18 (31.6%)	4 (22.2%)	2 (25.0%)
Available record (*n*)	1,754	381	14	37	57	18	8
3. Antidiabetic agent only, *n* (%)	0 (0.0%)	442 (50.8%)	4 (17.3%)	8 (16.7%)	8 (9.5%)	7 (28.0%)	2 (20.0%)
4. Lifestyle modification only, *n* (%)	0 (0.0%)	44 (5.1%)	5 (21.7%)	3 (6.2%)	19 (22.6%)	0 (0.0%)	0 (0.0%)

contribute to the increased numbers of patients with type 2 diabetes.

The average age of onset of type 1 diabetes (12.2 years) in the present study is comparable to that of previous studies from the USA, India and Malaysia (10.0–12.9 years)[17,21,22]. The EURODIAB ACE Study Group, SEARCH and YDR reported a peak incidence of type 1 diabetes from 10 to 14 years-of-age[17,22,23]. The present study showed the highest incidence of type 1 diabetes within the same age group (10 to <15 years), followed by 5 to <10 years, and ≤5 years. For type 2 diabetes patients, the mean age of onset ranged from 12 to 21.7 years in previous studies[17,21,22,24,25], the peak incidence was observed during 15–19 years[22], and just 8% were diagnosed at age <10 years[25]. In the present study, the mean age of type 2 diabetes onset was 20.8 years, the peak incidence occurred during 26–30 years and just 4.2% were aged <10 years at diagnosis. Our peak incidence was older compared with those reported from previous studies. This is likely due to our expanded inclusion criteria to the age of onset of <30 years.

Regarding presenting symptoms at diagnosis in type 1 diabetes patients, DKA was present in 35.1% and 28.7% in the SEARCH and YDR studies, respectively[26]. A systematic review that included 29,000 patients from 31 countries showed that the frequency of DKA at diagnosis of type 1 diabetes ranged from 12.8 to 80%. The highest frequencies were in the United Arab Emirates, Saudi Arabia and Romania, and the lowest frequencies were in Sweden, the Slovak Republic and Canada[27]. The frequency of DKA in those countries was found to be inversely associated with gross domestic product[27]. In type 2 diabetes, the prevalence of DKA at diagnosis in SEARCH and YDR were 5.5 and 6.6%, respectively[26]. The present study reported a higher prevalence of DKA at diagnosis in both type 1 diabetes and type 2 diabetes patients compared with SEARCH and YDR[26]. This might be explained by a relatively low incidence of young-onset diabetes in Thailand, which could result in relative non-familiarity with diabetes symptoms among parents and patients, and possibly also among physicians. Therefore, increased awareness of diabetes symptoms among the public and among healthcare professionals in Thailand is greatly needed to enhance early diagnosis and to prevent the development of DKA.

Glycemic control and insulin regimen in type 1 diabetes patients varies greatly among countries. The YDR study reported a mean HbA_{1c} of 11.0%, with 7.2% achieving the glycemic target (HbA_{1c} <7.5%), whereas the SEARCH study reported a mean HbA_{1c} of 7.8%, with 42% achieving the glycemic target[28]. In YDR, 52.8% of type 1 diabetes patients were on a once/twice daily regimen; however, 65.1% of patients in the SEARCH study were on a basal–bolus regimen[28]. The Australasian Diabetes Data Network reported that 27% of type 1 diabetes achieved the HbA_{1c} target, with a majority of patients treated with intensive insulin therapy[29]. In the present study, more than half of type 1 diabetes patients (55.2%) were receiving intensive insulin treatment; however, just 12.4% of our

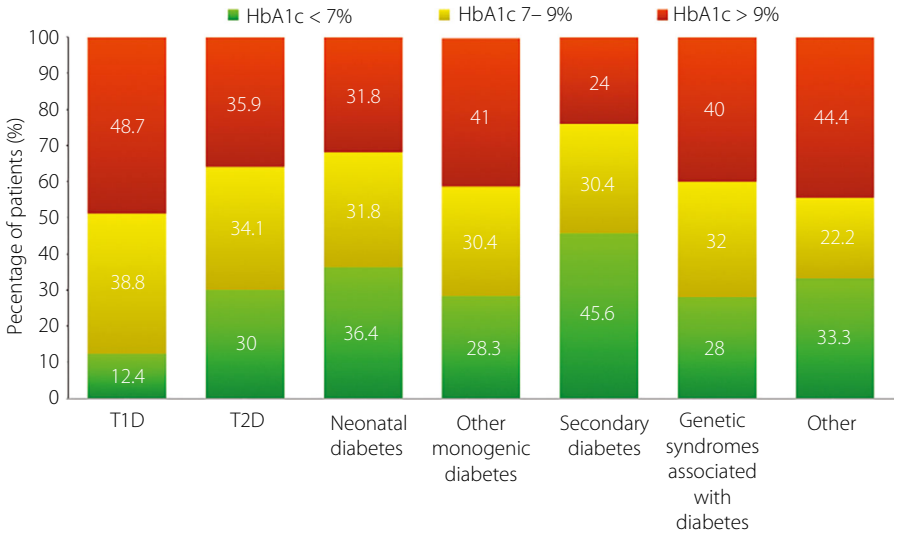


Figure 3 | Percentage of patients achieving different levels of glycated hemoglobin (HbA_{1c}) control compared among different types of diabetes. T1D, type 1 diabetes; T2D, type 2 diabetes.

type 1 diabetes patients achieved the recommended glycemic target of <7%[30,31].

Glycemic control among young type 2 diabetes patients also varies among countries. The YDR study reported a mean HbA_{1c} of 9.9%, with 18.1% achieving the glycemic target, whereas the SEARCH study reported a mean HbA_{1c} of 7.2%, with 67.7% achieving the glycemic target[28]. In YDR and SEARCH, 30–43% of type 2 diabetes patients were treated with metformin only, and 33–39% required insulin treatment[28]. Similar to the SEARCH study, the Pediatric Diabetes Consortium, which included young type 2 diabetes patients from 19 centers in the USA, reported an average HbA_{1c} of 7.8%, whereas the Pediatric Diabetes Prospective registries in Germany, Austria and Luxemburg reported a lower mean HbA_{1c} of 6.5%[24]. In the present study, 50% of type 2 diabetes patients were treated with an oral antidiabetic agent only. However, glycemic control among type 2 diabetes patients in the present cohort (mean HbA_{1c} 8.48%) was worse than reported from SEARCH, Pediatric Diabetes Consortium and Pediatric Diabetes Prospective registries[25,28], and just 30% of patients in the present study achieved the glycemic target. It has been shown that childhood-onset type 2 diabetes has a more progressive nature and higher rate of treatment failure[32] compared with adult-onset type 2 diabetes. The high proportion of patients in this registry that did not achieve glycemic target emphasizes the urgent need to develop a more effective nationwide strategy to improve care, education and support for patients with young-onset diabetes to reduce the burden of diabetes-related complications.

The present study had some limitations. First, this study had a retrospective design. Second, only patients from tertiary public hospitals were enrolled, so the results might not be representative of or generalizable to all of Thailand. It is possible that the higher numbers of patients diagnosed in recent years could be a true increase in the incidence, but we cannot exclude if those diagnosed earlier were lost to follow up nor could we confirm their vitality. It is possible that adult patients with young-onset diabetes were missed from this registry, as the year of diagnosis might have not been consistently recorded, resulting in an underestimation. Third, diagnosis of the different types of diabetes was based solely on clinical manifestation. Distinguishing among the different types of diabetes can be challenging. Diabetes autoantibodies and genetic testing were available in some patients only, potentially resulting in misclassification. Less than 20% of type 2 diabetes patients had diabetes autoantibodies measurement, possibly, some type 2 diabetes patients, requiring insulin treatment, might have latent autoimmune diabetes of adults[33] or a hybrid form of diabetes. Accordingly, to improve the accuracy of diabetes diagnosis and to provide the proper management, a genetic study evaluating the genetic causes of diabetes and diabetes autoantibodies has been implemented in Thailand as part of T1DDAR CN, and that study is ongoing.

In this registry, type 1 diabetes remains the most common type of diabetes among patients aged <20 years. The proportion of type 2 diabetes was found to increase substantially with age, and it has become more prevalent among patients with age of onset from 21 to 30 years. The increase in diabetes diagnoses in recent years might reflect an increase in diabetes incidence. The majority of patients in this registry did not achieve the glycemic target, especially the type 1 diabetes patients.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study protocol was approved by the Central Research Ethics Committee of Thailand, and by the institutional review board of each participating center.

Informed consent: Written informed consent or informed consent was not obtained, as this was a retrospective study.

Approval date of registry and the registration no. of the study/-trial: Approval date of Registry 11 July 2016, and approval number CREC 009/2559BRm.

Animal studies: All authors have confirmed that this study did not involve animal subjects.

REFERENCES

1. Patterson C, Guariguata L, Dahlquist G, *et al*. Diabetes in the young - a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract* 2014; 103: 161–175.
2. Pinhas-Hamiel O, Dolan LM, Daniels SR, *et al*. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr* 1996; 128: 608–615.
3. Reutrakul S, Deerochanawong C. Diabetes in Thailand: status and policy. *Curr Diab Rep* 2016; 16: 28.
4. Tuchinda C, Angsusingha K, Chaichanwalanakul K, *et al*. The epidemiology of insulin-dependent diabetes mellitus (IDDM): report from Thailand. *J Med Assoc Thai* 1992; 75: 217–222.
5. Tuchinda C, Likitmaskul S, Unachak K, *et al*. The epidemiology of type 1 diabetes in Thai children. *J Med Assoc Thai* 2002; 85: 648–652.
6. Likitmaskul S, Kiattisathavee P, Chaichanwatanakul K, *et al*. Increasing prevalence of type 2 diabetes mellitus in Thai children and adolescents associated with increasing prevalence of obesity. *J Pediatr Endocrinol Metab* 2003; 16: 71–77.
7. Dejkhamron P, Santiprabhob J, Likitmaskul S, *et al*. Type 1 diabetes management and outcomes: a multicenter study in Thailand. *J Diabetes Investig* 2021; 12: 516–526.
8. World Health Organization (WHO). Classification of Diabetes Mellitus. 2019.
9. Karaa A, Goldstein A. The spectrum of clinical presentation, diagnosis, and management of mitochondrial forms of diabetes. *Pediatr Diabetes* 2015; 16: 1–9.
10. Rigoli L, Di Bella C. Wolfram syndrome 1 and Wolfram syndrome 2. *Curr Opin Pediatr* 2012; 24: 512–517.
11. Plamper M, Gohlke B, Schreiner F, *et al*. Mecasermin in insulin receptor-related severe insulin resistance syndromes: case report and review of the literature. *Int J Mol Sci* 2018; 19: 1268.
12. Hamman RF, Bell RA, Dabelea D, *et al*. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. *Diabetes Care* 2014; 37: 3336–3344.
13. Divers J, Mayer-Davis EJ, Lawrence JM, *et al*. Trends in incidence of type 1 and type 2 diabetes among youths - selected counties and indian reservations, United States, 2002–2015. *MMWR Morb Mortal Wkly Rep* 2020; 69: 161–165.
14. Gomez-Lopera N, Pineda-Trujillo N, Diaz-Valencia PA. Correlating the global increase in type 1 diabetes incidence across age groups with national economic prosperity: a systematic review. *World J Diabetes* 2019; 10: 560–580.
15. Knip M. Type 1 diabetes in Finland: past, present, and future. *Lancet Diabetes Endocrinol* 2021; 9: 259–260.
16. Abela AG, Fava S. Why is the incidence of type 1 diabetes increasing? *Curr Diabetes Rev* 2021; 17: e030521193110.
17. Praveen PA, Madhu SV, Viswanathan M, *et al*. Demographic and clinical profile of youth onset diabetes patients in India-Results from the baseline data of a clinic based registry of people with diabetes in India with young age at onset-[YDR-02]. *Pediatr Diabetes* 2019; 22: 15–21.
18. Uchigata Y, Otani T, Takaike H, *et al*. Time-course changes in clinical features of early-onset Japanese type 1 and type 2 diabetes: TWMU hospital-based study. *Diabetes Res Clin Pract* 2008; 82: 80–86.
19. Lee EY, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. *Front Med* 2018; 12: 658–666.
20. Jensen ET, Dabelea D. Type 2 diabetes in youth: new lessons from the SEARCH study. *Curr Diab Rep* 2018; 18: 36.
21. Yeow TP, Aun E-Y, Hor CP, *et al*. Challenges in the classification and management of Asian youth-onset diabetes mellitus- lessons learned from a single centre study. *PLoS One* 2019; 14: e0211210.
22. Hockett CW, Praveen PA, Ong TC, *et al*. Clinical profile at diagnosis with youth-onset type 1 and type 2 diabetes in two pediatric diabetes registries: SEARCH (United States) and YDR (India). *Pediatr Diabetes* 2021; 22: 22–30.
23. Levy-Marchal C, Patterson C, Green A. Variation by age group and seasonality at diagnosis of childhood IDDM in Europe. The EURODIAB ACE Study Group. *Diabetologia* 1995; 38: 823–830.

24. Klingensmith GJ, Lanzinger S, Tamborlane WV, *et al*. Adolescent type 2 diabetes: comparing the pediatric diabetes consortium and Germany/Austria/Luxemburg pediatric diabetes prospective registries. *Pediatr Diabetes* 2018; 19: 1156–1163.
25. Klingensmith GJ, Connor CG, Ruedy KJ, *et al*. Presentation of youth with type 2 diabetes in the Pediatric Diabetes Consortium. *Pediatr Diabetes* 2016; 17: 266–273.
26. Praveen PA, Hockett CW, Ong TC, *et al*. Diabetic ketoacidosis at diagnosis among youth with type 1 and type 2 diabetes: results from SEARCH (United States) and YDR (India) registries. *Pediatr Diabetes* 2021; 22: 40–46.
27. Usher-Smith JA, Thompson M, Ercole A, *et al*. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. *Diabetologia* 2012; 55: 2878–2894.
28. Amutha A, Praveen PA, Hockett CW, *et al*. Treatment regimens and glycosylated hemoglobin levels in youth with Type 1 and Type 2 diabetes: Data from SEARCH (United States) and YDR (India) registries. *Pediatr Diabetes* 2021; 22: 31–39.
29. Phelan H, Clapin H, Bruns L, *et al*. The Australasian Diabetes Data Network: first national audit of children and adolescents with type 1 diabetes. *Med J Aust* 2017; 206: 121–125.
30. American Diabetes Association. Glycemic targets: standards of medical care in diabetes-2020. *Diabetes Care* 2020; 43: S66–S76.
31. DiMeglio LA, Acerini CL, Codner E, *et al*. ISPAD clinical practice consensus guidelines 2018: glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes* 2018; 19: 105–114.
32. Group TS, Zeitler P, Hirst K, *et al*. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012; 366: 2247–2256.
33. Jones AG, McDonald TJ, Shields BM, *et al*. Latent Autoimmune Diabetes of Adults (LADA) is likely to represent a mixed population of autoimmune (type 1) and nonautoimmune (type 2) diabetes. *Diabetes Care* 2021; 44: 1243–1251.

APPENDIX 1

The following persons participated in the T1DDAR CN:

Site/hospital name, city	Name
1. Central Region	
1.1 University hospitals	
HRH Princess Maha Chakri Sirindhorn Medical Center-MSMC Hospital, Nakhon Nayok	Nattakarn Wongjitrat
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

Appendix 1 (*Continued*)

Site/hospital name, city	Name
Vajira Hospital, Navamindradhiraj University, Bangkok	Natphassorn Dermkhuntod Petch Rawdaree Thanyaros Sinsophonphap Warunee Sunpakaew
1.2 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
1.3 Hospitals in the Ministry of Defense	
Bhumibol Adulyadej Hospital, Bangkok	Chulalak Nganlasome Karnsuda Pichetsin Kesinee Boonpakdee
Phramongkutklao Hospital, Bangkok	Jiraporn Nuphonthong Nattapol Sathavarodom Nawaporn Numbenjapon
Somdejprapinklao Hospital, Bangkok	Chantraporn Keamseng
2. North region	
2.1 University Hospitals	
Chiang Mai University Hospital, Chiang Mai	Danil Wongsa Laddawan Limpijankit Mattabhorn Phimphilai Prapai Dejkhamron
2.2 Hospitals in the Ministry of Public Health	
Buddhachinnaraj Hospital, Phitsanulok	Meijinee Densriwiwat
Chiang Rai Prachanukroh Hospital, Chiang Rai City	Kiran Sony Orathai Mahawongsanan Pataree Maneerat
Nakornping Hospital, Chiang Mai	Hataitip Tangngam Tattiwa Nirach
3. Northeast region	
3.1 University Hospitals	
Srinagarind Hospital, Khon Kaen University, Khon Kaen	Chatlert Pongchaiyakul Ouyporn Panamonta Pattara Wiromrat
3.2 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
Sunphasitthiprasong Hospital, Ubon Ratchathani	Jaturat Petchkul

Appendix 1 (*Continued*)

Site/hospital name, city	Name
4. East region	
4.1 University Hospitals	
Burapha University Hospital, Chonburi	Krittha Jeerawongpanich
4.2 Hospitals in the Ministry of Public Health	
Chonburi Hospital	Somlak Tongmeesee
Phrapokklao Hospital, Chanthaburi	Thapana Roonghiranwat
Rayong Hospital, Rayong	Chotima Sornsiriwong
	Naruewan Piriyabanjong
	Tippawan Kongvitayanon
5. South region	
5.1 University Hospitals	
Songklanagarind Hospital, Prince of Songkla University, Songkhla	Rattana Leelawattana
	Somchit Jaruratanasirikul
5.2 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 City	Palinee Nantarakchaikul