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Original Article

Association of diabetic ketoacidosis, severe hypoglycemia and glycemic control among children and young adults with type 1 diabetes mellitus treated with premixed versus basal-bolus insulin therapy

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ABSTRACT

Background: This study compared event rates of diabetic ketoacidosis (DKA) and severe hypoglycemia, as well as glycemic control, among children, adolescents, and young adults with type 1 diabetes mellitus (T1DM) receiving basal-bolus or premixed insulin therapy.

Methods: A total of 825 individuals aged ≤ 20 years with T1DM, using either basal-bolus or premixed insulin regimens, were retrospectively recruited from 2001 to 2015. Rates of DKA after diagnosis, severe hypoglycemia, and the level of glycated hemoglobin A1c (HbA1c) improvement during the follow-up period were analyzed.

Results: Of the 825 patients, 226 receiving a premixed regimen were matched to the same number of patients receiving a basal-bolus regimen. In the matched cohort, DKA (10.62% vs. 5.31%; $p = 0.037$) and severe hypoglycemic episodes (25.22% vs. 10.62%; $p < 0.001$) were significantly higher in patients receiving a premixed regimen than those receiving a basal-bolus regimen. The median reduction of HbA1c, compared to the treatment-naive level, was better with the basal-bolus regimen than with the premixed regimen in both matched (2.2 vs. 2.1; $p = 0.034$) and the entire (3.1 vs. 1.9; $p < 0.001$) cohorts. Regardless of insulin regimen, a higher HbA1c level was significantly linked to higher risk of DKA development (hazard ratio [HR] 1.35 per 1% increase; $p < 0.001$) once the HbA1c level was ≥7.5%.

Conclusions: A premixed insulin regimen may increase the DKA occurrence rate and severe hypoglycemic risk in children, adolescents, and young adults with TIDM, compared to a basal-bolus regimen. Tight glycemic control with HbA1c < 7.5% may prevent the increased risk of DKA.

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At a glance of commentary

Scientific background of the subject

Basal-bolus insulin regimen is closer to physiological requirement than premixed regimen. However, premixed regimen may provide more flexibility and freedom in clinical application. We aim to compare the event rate of acute complications such as severe hypoglycemia and DKA and the effect of glycemic control between the two regimens.

What this study adds to the field

Lines of evidence suggest that premixed insulin regimen may increase the DKA occurrence rate and severe hypoglycemic risk. Regardless of insulin regimen, tight glycemic control with HbA1c < 7.5% may prevent the increased risk of DKA.

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases caused by autoimmune destruction of insulin-producing pancreatic beta cells, and results in an absolute insulin deficiency. Three-quarters of cases of T1DM occur in children and young adults [1].

Diabetic ketoacidosis (DKA) is the most common acute complication of T1DM. Severe insulin deficiency will result in ketone formation, leading to ketoacidosis. Acute onset of DKA and the need for hospital admission can cause inconvenience and a real economic burden, not only to the patient but to the insurance company as well. According to a previous study, the incidence of DKA in children and young adults ranges from 4.8% to 5.2% per year [2–4]. The mortality rate in developing countries ranges from 6% to 24%, and is less than 1% in developed countries, and is expected to decrease in the future [5–7].

Insulin supplement therapy is the essential treatment option for patients with T1DM. Various insulin analogs with different combinations are the most recent regimen choices in treating T1DM. The basal-bolus regimen, 3 doses of preprandial ultra-short-acting insulin analogs with 1 dose of basal insulin per day, is closer to our physiologic insulin response [8] than other approaches. According to guidelines for managing T1DM in children and young adults from the National Institute for Health and Care Excellence (NICE), the American Diabetes Association (ADA), and the International Society for Pediatric and Adolescent Diabetes (ISPAD), patients should be treated with multiple daily injections of prandial insulin and basal insulin or with continuous subcutaneous insulin infusion [3,9,10]. However, 4 or more doses are usually an inconvenience for patients, especially children or young adults. In contrast, premixed insulin, which contains short- and intermediate-acting insulin, and which is given in 2–3 injections per day, may provide more flexibility and freedom while controlling the patient's glucose level.

Evidence proving that DKA is less likely to occur in patients treated with a basal-bolus analog regimen compared with patients treated with a premixed insulin analog regimen is limited or nearly unavailable. Because of ethical constraints, this issue is not easy to address in a prospective study. The causal relationship between insulin regimens and acute complications (such as severe hypoglycemia and DKA) is difficult to identify, due to low DKA event rate. Thus, we conducted a retrospective study via review of a longitudinal follow-up system. We hypothesized that a basal-bolus insulin regimen may lead to a lower event rate of DKA than a premixed regimen.

Methods

Data collection

Data of patients with T1DM contained in the Chang Gung Research Database were retrospectively reviewed and collected from the nationwide institutional branches of Chang Gung Memorial Hospital (CGMH), which are located in the northern, southern, and central parts of Taiwan. This registry database contains patients' medical records from the outpatient and admission departments and the emergency room at CGMH from January 2001 to June 2015. Diagnoses are registered using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Patient enrollment and selection

After obtaining approval from the local institutional review board of the Chang Gung Medical Foundation (IRB No. 201800079B0), cases of patients diagnosed with T1DM (ICD-9-CM: 250.01 or 250.03) were extracted from the database. Patients with three or more diagnostic codes (ICD-9-CM: 250.01 or 250.03) were classified as T1DM or one diagnostic code plus catastrophic illness certificate of T1DM. Certificates of catastrophic illnesses in Taiwan are carefully examined by specialists on the committee of the Bureau of National Health Insurance, which aims to lessen the financial burden of patients with certain diseases.

The basal-bolus regimen group was defined as patients using long-acting analogs (insulin detemir and insulin glargine), plus preprandial short-acting analogs (insulin glulisine [rDNA origin] injection [Apidra®, sanofi-adventis, Bridgewater, CT, USA]; insulin aspart [rDNA origin] injection [Aspart®, Novo Nordisk, Bagsvaerd, Denmark]; or insulin lispro injection [Humalog®, Eli Lilly and Co., Indianapolis, IN, USA]. Patients in the premixed regimen group were defined as those using biphasic insulin analogs (e.g., NovoMix® 30 [Novo Nordisk], Novomix® 50, Humalog®25, and Humalog® 50 [Eli Lilly and Co.]), injected 2 to 3 times daily. The index date was defined as the date of the first T1DM diagnosis and 30 days of insulin exposure. The follow-up period was the time interval from the index date to the date of a DKA episode or until June 30, 2015. Patients who met any of the following criteria were excluded from the study: (a) age >20 years at the index date, (b) age <6 months at the index date, (c) used neither premixed nor basal-bolus regimens during the follow-up period, (d) crossover using the two regimens, (e) a DKA episode before the index date, and (f) missing data, as shown in Fig. 1.

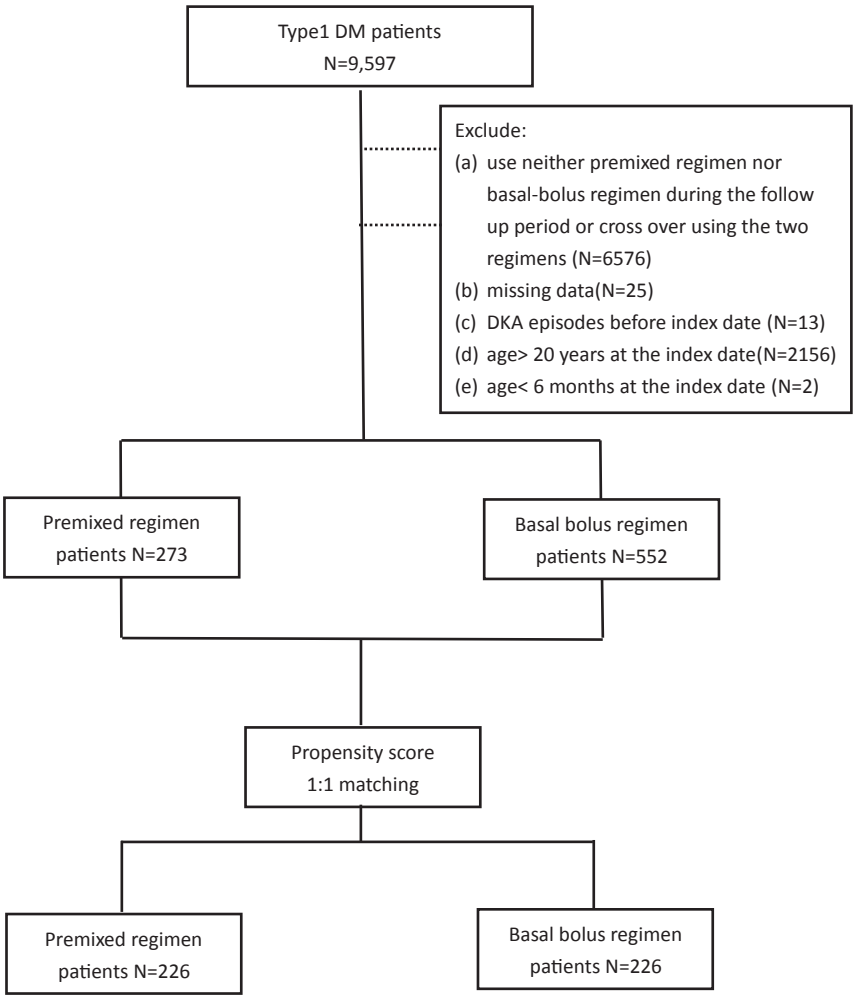

Fig. 1 Flowchart of the cohort study.

Outcomes

Primary outcomes were the occurrence of DKA after a T1DM diagnosis had been made. DKA was defined based on both ICD9-CM codes and laboratory data. The laboratory criteria included venous blood pH of <7.30, ketonemia, or ketonuria [10], and the need for hospital admission and treatment. Secondary outcomes were severe hypoglycemia and reduced HbA1c levels during the follow-up period. Severe hypoglycemia was defined when the patient required assistance from another person to actively administer carbohydrates and glucagon or to take other corrective actions [11]. Reduced HbA1c level was defined as the difference between the first HbA1c level after the index date and the mean HbA1c level throughout the follow-up period.

Matching and weighting

The premixed insulin group was matched with the basal-bolus group with a 1:1 ratio based on age, gender, and mean HbA1c level; propensity score matching was used to minimize potential selection bias that might influence the study outcome. We also performed analyses with inverse probability of treatment weighting, using the propensity score to estimate the association between insulin regimens and outcomes, including all eligible patients (the entire cohort).

Statistical analysis

Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). Clinical characteristics between these two study groups, including age, gender, follow-up period, HbA1c level at baseline, and mean HbA1c throughout the study were compared using the chi-square test for categorical variables and nonparametric analysis for continuous variables. Time-to-event outcomes (DKA episodes) were analyzed by predefined periods, from 6 months until the final follow-up for each study group (premixed and basal-bolus group) using the Kaplan–Meier method. Cox proportional hazards regression with propensity score weighting analyses adjusted for age, gender and insulin regimen was used in the entire cohort to evaluate the efficacy of each HbA1c condition. Significance was set at $p < 0.05$, and 95% confidence intervals (CI) were quoted throughout the study.

Table 1 Characteristics of the study patients before and after propensity score matching.

Characteristic	Matched cohort			Entire cohort		
	Premixed n = 226	Basal n = 226	*p*-value	Premixed n = 273	Basal n = 552	*p*-value
Age						
Median (IQR), year	13.3 (10.6–16.5)	13.3 (10.7–16.8)	0.927	13.5 (10.4–16.9)	11.8 (8.5–14.8)	<0.001*
Gender, no. (%)			1.000			0.221
Female	121 (53.5)	121 (53.5)		142 (52.0)	312 (56.5)	
Male	105 (46.5)	105 (46.5)		131 (48.0)	240 (43.5)	
Follow-up period						
Median, year	9.3 (6.4–12.3)	8.4 (3.9–12.1)	0.025*	9.5 (6.5–12.3)	7.9 (4.1–11.5)	<0.001
HbA1c						
Baseline, median (IQR), %	11.5 (9.0–14.0)	12.2 (9.4–14.4)	0.074	12.2 (9.6–14.3)	12.4 (9.6–14.4)	0.411
Average, median (IQR), %	9.5 (8.3–10.6)	9.3 (8.3–10.4)	0.546	9.8 (8.5–11.1)	8.6 (7.8–9.8)	<0.001*

Continuous data are expressed as median and interquartile range(IQR); categorical data are expressed as percentage (%).
Abbreviations: IQR: interquartile range; HbA1c: glycated hemoglobin A1c; *p value < 0.05 in 95% confidence interval.

Results

Demographic description

Among the 825 eligible patients with T1DM, 273 were classified in the basal-bolus group and 552 in the premixed insulin group. After propensity score 1:1 matching with age, gender, and mean HbA1c level, 226 patients were selected from each treatment group. Table 1 summarizes their demographic data.

In the entire cohort, female gender was predominant in both groups, but this was not statistically significant (52.0% vs. 56.5%, respectively; $p = 0.221$). The median age was 13.5 years (interquartile range [IQR], 10.4–16.9 years) in the premixed group, who were older than 11.8 years (IQR, 8.5–14.8 years) in the basal-bolus group ($p < 0.001$). The median follow-up period was 9.5 years (IQR, 6.5–12.3 years) in the premixed insulin group and 7.9 years (IQR, 4.1–11.5 years) in the basal-bolus group ($p < 0.001$). The baseline median HbA1c level was 12.2% (IQR, 9.6% to 14.3%) in the basal-bolus group and 12.4% (IQR, 9.6 to 14.4) in the premixed insulin group without statistically difference ($p = 0.411$). The median average HbA1c level (throughout the follow-up period) was 8.6% (IQR, 7.8%–9.8%) in the basal-bolus group, which was lower than the 9.8% (IQR, 8.5%–11.1%) reported in the premixed insulin group ($p < 0.001$) (Table 1).

In the matched cohort, the median duration of premixed and basal-bolus insulin therapies was 9.3 years (IQR, 6.4 years–12.3 years) and 8.4 years (IQR, 3.9 years–12.1 years), respectively ($p = 0.025$). Otherwise, all parameters such as gender, age, baseline HbA1c and average HbA1c levels were insignificantly different between the two groups (Table 1).

Primary outcome

Table 2 shows the primary outcomes for the entire cohort. In the matched cohort, 36 DKA events occurred in 452 patients (total event rate, 8.0%). DKA events occurred in 24 of 226 patients (10.6%) in the premixed insulin group, and 12 of 226 patients (5.3%) in the basal-bolus group. The risk of DKA event rates increased in the premixed insulin group ($p = 0.037$).

In the entire cohort, the total event number of DKA events was 54 in 825 patients: 29 of 273 (10.6%) in the premixed group and 25 of 552 (4.5%) in the basal-bolus group. The risk of DKA significantly increased in the premixed insulin group ($p < 0.001$). Results among the matched and entire cohorts were similar.

Fig. 2 shows the cumulative probability of DKA in the two study groups. In the matched cohort, the premixed insulin group had 6 DKA events in the first month, whereas the basal-bolus group had no DKA events in the first month (Fig. 2A). The premixed insulin group had a higher cumulative probability of a DKA event throughout the follow-up period in both cohorts (Fig. 2B–D).

After adjusting for the type of insulin, age, and gender, the HbA1c level significantly influenced the risk of DKA (hazard ratio [HR] 1.35, 95% CI 1.21–1.51; $p < 0.001$) (Table 3,

Table 2 Event numbers of the primary outcome and secondary outcome between the study cohorts.

Outcome	Matched cohort			Entire cohort		
	Premixed n = 226	Basal bolus n = 226	*p*-value	Premixed n = 273	Basal bolus n = 552	*p*-value
Diabetic ketoacidosis						
Event, no. (%)	24 (10.6)	12 (5.3)	0.037*	29 (10.6)	25 (4.5)	<0.001*
Participants with ≥1 episode of hypoglycemia						
Event (%)	57 (25.2)	24 (10.6)	<0.001*	70 (25.6)	56 (10.1)	<0.001*
HbA1c reduction						
Median (IQR), %	2.1 (0.3–4.5)	2.2 (0.2–5.1)	0.034*	1.9 (0.0–4.2)	3.1 (0.7–5.7)	<0.001*

HbA1c glycated hemoglobin A1c, SD standard deviation, *p value < 0.05.
Abbreviations: IQR: interquartile range; HbA1c: glycated hemoglobin A1c; * p-value <0.05 in 95% confidence interval.

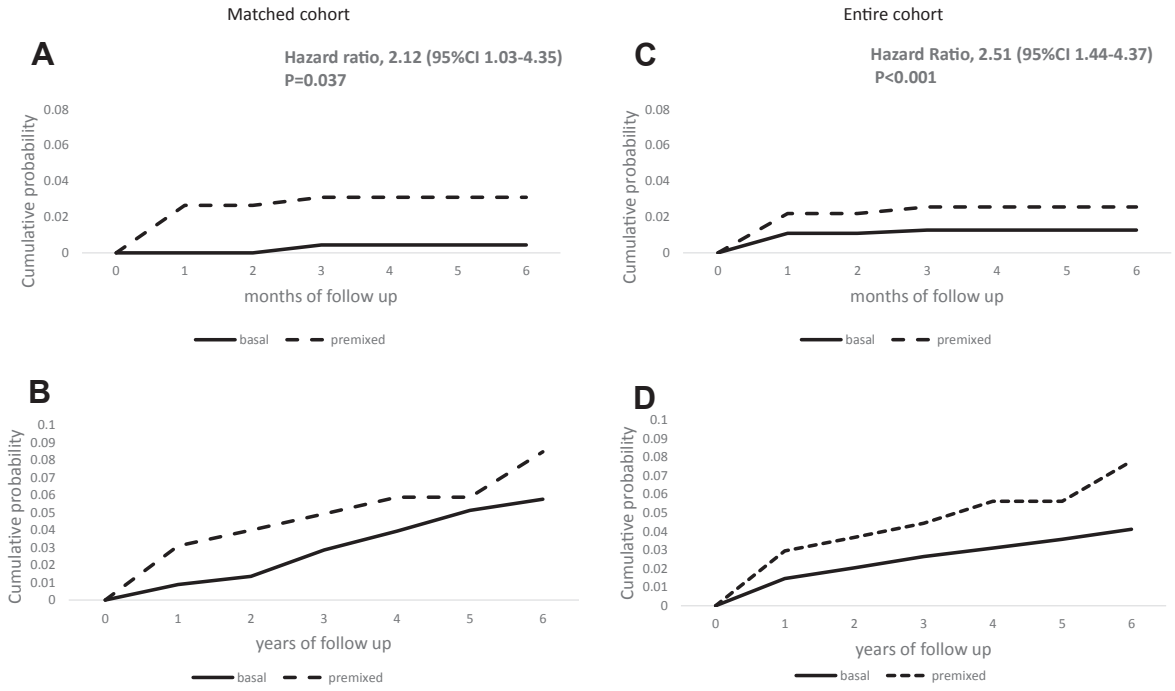

Fig. 2 **Cumulative probability of event rates in each study group for DKA.** Cumulative probability of DKA event rates in each study group for: (A) matched cohort in 6 months, (B) matched cohort in 6 years, (C) entire cohort in 6 months, and (D) entire cohort in 6 years. The cumulative probability of DKA in the premixed insulin group was higher than in the basal-bolus group in the first few months.

model 1). Per 1% increase in HbA1c level, the HR of DKA also increased by 35%. Furthermore, five different HbA1c levels (models 2–6) were established to determine the optimal control level that would prevent the increased risk of DKA. HbA1c levels of ≥7.5% (models 2–5) significantly increased the risk of DKA.

Table 3 The risk of development of DKA in different level of glycohemoglobin.

	HR	95% CI	*p*-value
Model 1			
HbA1c ↑ 1%	1.35	(1.21–1.51)	<0.001
Model 2			
HbA1c ≥ 9.0	4.90	(2.63–9.17)	<0.001
Model 3			
HbA1c ≥ 8.5	4.31	(2.11–8.77)	<0.001
Model 4			
HbA1c ≥ 8.0	3.79	(1.63–8.77)	0.002
Model 5			
HbA1c ≥ 7.5	3.79	(1.18–12.20)	0.025
Model 6			
HbA1c ≥ 7.0	5.24	(0.72–38.46)	0.101

Different HbA1c levels (model 2–6) used Cox proportional hazards regression with propensity score weighting analyses adjusted for potential confounders that influenced DKA occurrence. All models were adjusted for age, gender, and insulin regimen, plus different HbA1c conditions. Abbreviations: HR: hazard ratio; CI: confidence interval; DKA: diabetic ketoacidosis; HbA1c: glycated hemoglobin A1c.

Secondary outcome

Table 2 shows the data on severe episodes of hypoglycemia and reduced HbA1c level. In the matched cohort, 57 of the 226 patients in the premixed group experienced more than one severe episode of hypoglycemia, which is higher than that of 24 of 226 patients in the basal-bolus group (25.2% vs. 10.6%, respectively; $p < 0.001$). A similar result was observed in the entire cohort. A total of 70 out of 273 patients in the premixed insulin group and 56 of the 552 in the basal-bolus insulin group had at least one episode of severe hypoglycemia (25.6% vs. 10.1%, respectively; $p < 0.001$).

In the entire cohort, better glycemic improvement, as evidenced by a greater reduction in HbA1c level was observed in the basal-bolus insulin group (3.1, IQR, 0.7 to 5.7) than in the premixed insulin group (1.9, IQR, 0.0 to 4.2) ($p < 0.001$). In the matched cohort, the degree of HbA1c reduction was 2.2% (IQR, 0.2 to 5.1) in the basal-bolus group, which was greater than 2.1% (IQR, 0.3 to 4.5) in the premixed group ($p = 0.034$), indicating a better HbA1c reduction in the basal-bolus insulin group in both cohorts.

Discussion

This longitudinal retrospective study investigated the association between DKA and two different insulin regimens (premixed insulin and basal-bolus insulin regimens). Although the evidence that various insulin regimens may alter the risk of

DKA was not proposed by the NICE guideline [10], we found different risks of DKA existed between various insulin regimens; that is, the premixed insulin regimen might influence the increased DKA risk in children and young adults with T1DM.

Regardless of the absence of a head-to-head study, a small Canadian study showed seven times more DKA incidents in children with poorly controlled T1DM when treated with premixed insulin. The report did not give a specific explanation for the difference between groups [12]. Although concrete reasons for DKA risk in patients treated with premixed insulin may be difficult to identify, we tried to explore the underlying causes of DKA risk factors.

Many studies have reported that a high HbA1c level is an important risk factor for DKA in children with T1DM. In a prospective cohort study, Rewers et al. reported an estimated risk of 1.43–1.68-fold DKA incidence per 1% HbA1c increase in children with T1DM [13]. Another cross-national registration study that analyzed 49,859 cases of pediatric T1DM also revealed a high odds ratio of DKA in those with elevated HbA1c (OR 2.54, 95% CI 2.09–3.09 for HbA1c from 7.5 to <9% and OR 8.74, 95% CI 7.18–10.63 for HbA1c $\geq$ 9.0%) [14]. Our study also showed similar results: we found a 35% increase in the HR for DKA per 1% HbA1c elevation. Thus, a higher HbA1c level is associated with higher risk of DKA.

We have learned from the results of the Diabetes Control and Complications Trial (DCCT) that intensive therapy, administered either with an external insulin pump or by 3 or more daily insulin injections, provides better glycemic control than does conventional treatment with 1 or 2 daily insulin injections [15]. In an Irish study, higher HbA1c levels were observed in young type 1 diabetic patients treated with premixed insulin than in those treated with a basal-bolus insulin regimen (8.4 $\pm$ 0.5% versus 6.9 $\pm$ 0.2%, $p < 0.01$) [16]. Similarly, HbA1c levels were significantly higher in children treated with purely premixed insulin in a French survey enrolling 7206 children with T1DM. The children were attending a diabetes summer camp, and were classified into six main types of regimens based on insulin type and injection timing [17]. Clinically, the HbA1c level was better controlled by switching from premixed insulin to a basal-bolus regimen, not only in patients with T1DM but also in patients with T2DM [18,19]. In our study, we also observed better HbA1c control in the basal-bolus insulin group than in the premixed insulin analog regimen group. Since a higher HbA1c level may indicate higher risk of DKA, this may also explain why the DKA risk was higher in patients treated with premixed insulin analogs.

Furthermore, the rate of insulin titration may be another important issue. In a previous study, a group receiving a premixed insulin regimen had higher HbA1c levels and slower insulin titration rates in a randomized, cross-over trial of both T1DM and T2DM patients [20]; therefore, patients treated with a premixed insulin regimen required more time to reach the ideal HbA1c target. However, most of the DKA events occurred within the first few months, especially during the first month, in our study. The difference of DKA cumulative probability between the two groups also appeared early in the first month and first year, respectively (Fig. 2). The early DKA cumulative probability difference and slower titration rate in those receiving a premixed insulin regimen might result in the increased trend of DKA.

In addition, approximately 28%–65% of instances of DKA occurred in young T1DM patients due to omitted insulin injections; therefore, omitting insulin injection is the major cause of DKA in children and young adults with T1DM [13,21–25]. In patients with T1DM, after 4–6 h of withdrawal from insulin administration ketone bodies will increase, which eventually increases the risk of DKA [26,27].After premixed insulin injection, serum insulin concentration may reach its maximum level 60–100 min after injection and down to relatively low level after around 15–18 h [28–31]. If patients miss one dose of premixed insulin injection, it means not only losing one-third to one-half of the total daily insulin dose, but also means exposing the patient in a relative or absolute insulin deficiency period, which would increase the risk of DKA.

We found a good correlation between HbA1c level and DKA risk only when the HbA1c was $\geq$7.5% according to the Cox regression hazard model (Table 3). Thus, similar to the ADA and ISPAD recommended guidelines [32,33], HbA1c should be maintained <7.5% in children and young adults with T1DM, to reduce the risk of DKA.

Hypoglycemia is the major concern in patients receiving insulin treatment. However, no clear or solid evidence showed that different insulin analog regimens altered hypoglycemia risk in children and adolescent with type 1 diabetes mellitus. Using the NICE guideline, two small studies enrolled a total of 166 children and adolescents with T1DM; the study results revealed increased hypoglycemia risk among those who used a premixed insulin regimen [10,34,35]. Our study had similar results. Compared with a premixed regimen, a basal-bolus regimen produced fewer variations in glucose levels [20], and might also have led to lower risk of hypoglycemia.

This study had several limitations. First, it was a retrospective study with several factors that might have interfered with some of the outcomes; these factors include ethnic records, immigration background, psychological disorders, total daily insulin dose, body weight record, and socioeconomic status. None of these are available in the Chang Gung Research Database. Second, the frequencies of self-monitored blood glucose level were also unavailable in the registry database. Third, although the number of patients was limited, patients who have multiple events might have been omitted in this study, because further follow-up after the first event was not performed. Fourth, we did not include patients who were receiving insulin pump therapy or continuous glucose monitoring, since both factors may lower the risk of DKA and hypoglycemia. Last, we may have missed some DKA events that were not recorded in our database because this is a single medical center study instead of a nationwide study.

Conclusions

Finally, we concluded that (1) patients receiving a basal-bolus regimen have lower DKA and severe hypoglycemia rates than do patients receiving premixed insulin regimen; (2) HbA1c should be maintained at <7.5%, just like the ADA and ISPAD recommendations, to reduce the risk of DKA; and, finally (3) a basal-bolus insulin regimen may be the treatment of choice

for children and young adults with T1DM. However, insulin therapy should be individualized for each diabetic patient; a premixed insulin regimen may be chosen as an alternative option to conveniently maintain a normal social relationship. Since DKA risk difference appeared early, doctors and other healthcare providers should monitor and educate the patients on premixed insulin regimens and how to prevent DKA, especially in the first few months of treatment.

Conflicts of interest

The authors declare that they have no competing interests.

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