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Association of diabetic ketoacidosis and HbA1c at onset with year-three HbA1c in children and adolescents with type 1 diabetes: Data from the International SWEET Registry

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Abstract

Objective: To establish whether diabetic ketoacidosis (DKA) or HbA1c at onset is associated with year-three HbA1c in children with type 1 diabetes (T1D).

Methods: Children with T1D from the SWEET registry, diagnosed <18 years, with documented clinical presentation, HbA1c at onset and follow-up were included. Participants were categorized according to T1D onset: (a) DKA (DKA with coma, DKA without coma, no DKA); (b) HbA1c at onset (low [<10%], medium [10 to <12%],

ABBREVIATIONS: BMI, Body mass index; BMI-SDS, Body mass index SD Score; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; HbA1c, glycated hemoglobin; ISPAD, International Society for Pediatric and Adolescent Diabetes; LOESS, locally estimated scatterplot smoothing; MOM, multiple of the mean; PGCS, Pediatric Glasgow Coma Scale; SAS, statistical analysis software; SH, severe hypoglycemia; SWEET, Better control in pediatric and adolescent diabete**S**: **W**orking to cr**E**ate C**E**n**T**ers of reference; T1D, Type 1 diabetes; WHO, World Health Organization.

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high [≥12%]). To adjust for demographics, linear regression was applied with interaction terms for DKA and HbA1c at onset groups (adjusted means with 95% CI). Association between year-three HbA1c and both HbA1c and presentation at onset was analyzed (Vuong test).

Results: Among 1420 children (54% males; median age at onset 9.1 years [Q1;Q3: 5.8;12.2]), 6% of children experienced *DKA with coma*, 37% *DKA without coma*, and 57% *no DKA*. Year-three HbA1c was lower in the *low* compared to *high* HbA1c at onset group, both in the *DKA without coma* (7.1% [6.8;7.4] vs 7.6% [7.5;7.8], $P = .03$) and in the *no DKA* group (7.4% [7.2;7.5] vs 7.8% [7.6;7.9], $P = .01$), without differences between *low* and *medium* HbA1c at onset groups. Year-three HbA1c did not differ among HbA1c at onset groups in the *DKA with coma* group. HbA1c at onset as an explanatory variable was more closely associated with year-three HbA1c compared to presentation at onset groups ($P = .02$).

Conclusions: Year-three HbA1c is more closely related to HbA1c than to DKA at onset; earlier hyperglycemia detection might be crucial to improving year-three HbA1c.

KEYWORDS
children, diabetic ketoacidosis, metabolic control, type 1 diabetes

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening complication of new-onset type 1 diabetes (T1D) in children and has a wide range of incidence worldwide, varying from 13% to 80%.[1,2] The incidence of DKA is moderate and stable in Germany (21.1%),[3] Austria (37.2%),[4] USA (30%),[5] UK (25%),[6] New Zealand (27%),[7] and Poland (25%).[8] Comparatively, the rates are highest in France (43.9%)[9] and Brazil (42%)[10] and reach alarming levels in the third world, Africa (71.1%-88%).[11] The lowest rates are in some select groups from first world countries, namely under longitudinal follow-up in Sweden (16%), Ontario, Canada (18.6%), Finland (19.4%), and Denmark (17.9%).[12,13] It is well-known that there is a negative correlation between background incidence of T1D and the frequency of DKA at onset.[14] However, even within similar geographical regions, DKA rates can vary, as shown in the Italian population under 15 years of age: the frequency of DKA was 41.9%, but much lower in Sardinia (23.6%), comparable to that reported in countries with a high incidence of T1D, due to the high level of suspicion in this region.[15] Lower residual β-cell function and poorer glycemic control during the following 1 to 2 years have been shown in children with DKA at presentation.[13,16] What remains to be further examined is whether it is chronic hyperglycemia (glycated hemoglobin [HbA1c]) or DKA at diagnosis that is the most important variable determining the following metabolic control. Viswanathan et al (2011) showed that HbA1c levels at onset might predict future metabolic control, however, the study was relatively small (120 children).[17] Similar results were partly confirmed by Nilsson et al (2017) showing that high HbA1c at onset was associated with high HbA1c during follow-up.[18] A retrospective analysis from the UK showed that tracking of HbA1c values occurs at all levels of HbA1c, such that children who reach HbA1c target early in the course of the disease are more likely to continue with low HbA1c levels.[19] Hofer et al (2014) similarly confirmed in an Austrian/German multicenter setting the evidence for long-term tracking of metabolic control from childhood until adulthood.[20]

SWEET (Better control in Pediatric and Adolescent diabete**S**: **W**orking to cr**E**ate C**E**n**T**ers of Reference) comprises a large multinational consortium of pediatric diabetes clinics worldwide collecting diabetes-related information on patients in a standardized database.[21,22] This study then represents a unique opportunity to evaluate a heterogeneous group of children with T1D worldwide and to examine the relationships between HbA1c and DKA at onset and subsequent metabolic control during the first and the third year after diagnosis and whether third-year HbA1c is more closely associated to DKA or HbA1c at onset.

2 | RESEARCH DESIGN AND METHODS

2.1 | Data sources and subjects

This analysis is based on data from the international, prospective, multicenter, standardized diabetes registry SWEET. Currently, 78 centers from five continents (47 from Europe) are included. All contributing centers meet specific entry criteria and are compliant with the International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice guidelines and the national database security and ethical

requirements.[22-24] As of September 2018, the SWEET database included 49 224 patients with 554 487 visits.

This is a multi-centered, register-based, cross-sectional observational, descriptive study from the SWEET database. Subjects with T1D, diagnosed before 18 years, with documented clinical presentation and HbA1c at onset and follow-up data available during the first and the third year after diagnosis were included. T1D was defined using the ISPAD clinical presentation guidelines.[25] Centers of the Asian/African region were excluded because data might not be representative due to the low number of patients (<20 subjects). The full study cohort, which included all patients with reported presentation at onset, consisted of 2932 youths with T1D treated in 29 centers from 17 European countries and six countries outside Europe (Figure S1). In a sub-analysis, children with documented HbA1c at onset were analyzed (n = 1420).

2.2 | Outcome variables

The SWEET dataset considers five categories of presentation at T1D onset: DKA with coma, DKA without coma, ketosis, hyperglycemia, or by screening. The most severe category which applied to the patient was used. DKA is defined according to the ISPAD guidelines (pH < 7.3 or bicarbonate <15 mmol/L).[26] Coma was defined clinically (*Pediatric Glasgow Coma Scale* [PGCS]). In this analysis, presentation at onset was classified as *DKA with coma*, *DKA without coma* or *no DKA*. Metabolic control was assessed by HbA1c, which was measured locally in each center. In order to adjust for differences among laboratories, a multiple of the mean (MOM) method was used, to mathematically standardize HbA1c values to the reference range of the Diabetes Control and Complications Trial (DCCT, 21-43 mmol/mol [4.05-6.05%]).[27] Any use of insulin pump was defined as pump treatment. Body mass index (BMI) was calculated as weight in kilogram divided by height squared in meters. BMI SD score (BMI *z*-score) was calculated using the World Health Organization (WHO) reference.[28] DKA beyond onset was defined according to the ISPAD guidelines and severe hypoglycemia (SH) was defined as an event that led to alterations in consciousness and required the assistance of another person.[26,29] Data was aggregated per patient during the first and third year after T1D diagnosis. Onset was defined as the first 10 days after T1D manifestation.

Four geographic regions were defined based on a combination of location and number of centers: (a) **Northern Europe**: Austria, Czech Republic, France, Denmark, Germany, Lithuania, Luxembourg, Netherlands, Poland, Sweden; (b) **Southern Europe**: Bulgaria, Croatia, Greece, Hungary, Portugal, Serbia, Spain; (c) **Australia/New Zealand**; and (d) **America/Canada**: US, Canada, Argentina, Costa Rica.

Eligible patients were divided into three groups based on age at onset: <6 years, 6 to <12 years, 12 to ≤18 years. In the sub-cohort of patients with documented HbA1c at onset, HbA1c at onset was divided into three groups: *low* < 10% (<86 mmol/mol); *medium* 10 to <12% (86 to <108 mmol/mol); and *high* ≥ 12% (≥ 108 mmol/mol).

2.3 | Statistical analysis

Data were summarized using median with quartiles for continuous variables or proportion for binary variables. Wilcoxon, Kruskal-Wallis or χ2-tests were used to analyze differences among groups. *P* values were corrected by Bonferroni-Holm method to adjust for multiple testing.

Among the presentation at onset groups, curves of HbA1c per month during the first year after T1D onset were estimated using locally weighted scatterplot smoothing (LOESS). Analyzing differences in HbA1c among presentation at onset groups for months 4 to 12 after diagnosis, a regression model taking into account multiple measurements was applied, which was adjusted for age at onset, gender and region.

Analyzing the third year after diagnosis, linear and logistic regression models were applied to adjust for confounders. In order to address variation among diabetes centers, region was entered as a fixed covariate. Moreover, models were adjusted for age at onset groups and gender. A model for the year-three HbA1c with additional adjustment for BMI-SDS and insulin dose was implemented. An additional model with an interaction term between presentation at onset group and HbA1c at onset group was applied. To adjust for multiple comparisons, Tukey-Kramer test was used. Results are presented as adjusted means with 95% confidence intervals (CI). Vuong test was employed in order to compare a model with HbA1c at onset groups versus a model with presentation at onset groups, to ascertain which one as explanatory variable was closer to the true distribution of the data of year-three HbA1c. Vuong test is probabilistic, based on H_0 (both models are equally close to the true distribution of data) against the alternative hypothesis that one model is closer.[30]

A two-sided *P* value < .05 was defined as statistically significant. All analyses were performed with Statistical Analysis Software 9.4 (SAS, SAS Institute Inc. Cary, North Carolina).

3 | RESULTS

The entire study cohort included 2932 children (53% male) with 1942 patients from Europe, 246 from Australia/New Zealand and 744 from America/Canada. Table 1 includes demographics and clinical parameters among the full cohort, the sub-cohort with documented HbA1c at onset (n = 1420), and for boys and girls separately.

3.1 | DKA with coma, DKA without coma, and no DKA groups

In the full cohort, 16% of children had *DKA with coma* at T1D onset, 27% *DKA without coma* and 57% *no DKA*. Table 2 includes baseline demographics and clinical parameters among presentation at onset groups.

There was no difference in clinical presentation at onset groups between boys and girls. Overall there was no difference in age at

TABLE 1 Demographics and clinical parameters of the study cohort and the sub-cohort of children with documented HbA1c at onset[a]

Variable	All	Boys	Girls	HbA1c at onset available	Boys	Girls
N	2932	1554	1378	1420	767	653
Age (years) at onset	9.2 [5.7;12.1]	9.4 [5.6;12.4]	8.9 [5.8;11.6]	9.1 [5.8;12.2]	9.5 [5.9;12.5]	8.7 [5.7;11.6]
0-<6 years (%)	27	27	27	27	26	28
6-<12 years (%)	48	45	51	47	44	49
12-≤18 years (%)	25	28	23	26	30	23
Males (%)	53			54		
Northern Europe (%)	48	48	46	70	70	69
Southern Europe (%)	19	19	19	24	24	24
Australia/New Zealand (%)	8	8	9	0	0	0
America/Canada (%)	25	25	26	6	6	7
Presentation at onset						
DKA with coma (%)	16	16	17	6	6	7
DKA without coma (%)	27	27	27	37	37	38
No DKA (%)	57	57	56	57	57	55
Clinical parameters at onset						
HbA1c (%) at onset				11.5 [10.1; 13.3]	11.2 [10.0; 12.9]	12.0 [10.3; 13.7]
BMI-SDS at onset				−0.32 [−1.17; 0.65]	−0.26 [−1.22; 0.67]	−0.37 [−1.06; 0.61]
Clinical parameters during third year after onset						
Year-three HbA1c (%)	7.7 [6.9; 8.5]	7.6 [6.9; 8.5]	7.7 [7.0; 8.6]	7.4 [6.8; 8.1]	7.3 [6.7; 8.1]	7.4 [6.8; 8.1]
Year-three BMI-SDS	0.60 [−0.07; 1.27]	0.56 [−0.12; 1.30]	0.64 [0.00; 1.23]	0.56 [−0.10; 1.17]	0.48 [−0-16; 1.23]	0.65 [−0-01; 1.16]
Therapy						
Insulin pump first year (%)	27	27	27	23	23	24
Insulin pump third year (%)	40	39	42	37	36	38

[a]Descriptive data were summarized using median [Q1;Q3] for continuous variables or proportion (%) for binary variable.

onset groups distribution by the presentation at onset; however, *DKA with coma* tended to be more common at T1D onset in children aged 6-12 years, while *DKA without coma* tended to be more common in children below 6 years of age and T1D with *no DKA* in subjects between 12 and 18 years of age (Table 2).

There was variation in regions distribution across the DKA groups ($P < .01$), (Table 2). While in Northern Europe *DKA with coma* was only present in 4.7% of children and the largest proportion of children presented with *no DKA* (60.7%), in the American/Canadian region *DKA with coma* was more frequent (40%) and fewer children (46.3%) presented with *no DKA*. In Southern Europe and Australia/New Zealand the distribution among presentation at onset groups was comparable to the full study cohort.

3.2 | First year after diagnosis

HbA1c was higher in the *DKA with coma* group compared to the other groups throughout the first year of diabetes (both $P < .01$), even after adjustment for demographics (Figure 1). HbA1c was not significantly different between *DKA without coma and no DKA* groups. HbA1c nadir value was reached simultaneously in the three groups during the fourth month after diagnosis, with the lowest value in the group with *no DKA*. Afterwards, HbA1c increased in all three groups.

3.3 | Third year after diagnosis

Year-three HbA1c and clinical data is presented in Table 2 according to presentation at onset groups and the results of clinical variables adjusted for demographics (age at onset, gender and region) are presented in Table S1.

3.3.1 | Association of DKA at onset-year-three HbA1c

The highest year-three HbA1c was observed in *DKA with coma* group compared to both the *DKA without coma* group and the *no DKA* group

TABLE 2 Demographics and clinical parameters during the third year among presentation at onset groups[a]

Variable	DKA with coma	DKA without coma	No DKA	*P* value
N	483	792	1657	
Males (%)	16.1	27.0	56.9	**<.01**
Females (%)	16.9	26.9	56.2	
Age (years) at onset	9.1 [5.8; 11.7]	9.2 [5.2; 12.1]	9.2 [5.9; 12.2]	n.s.
0-<6 years (%)	16.5	29.7	53.8	
6-<12 years (%)	17.8	25.5	56.7	
12-≤18 years (%)	13.9	27.1	59.0	
Northern Europe (%)	4.7	34.6	60.7	**<.01**
Southern Europe (%)	15.7	23.9	60.4	
Australia/New Zealand (%)	13.8	31.3	54.9	
America/Canada (%)	40.0	13.7	46.3	
Clinical parameters during the third year				
HbA1c (%)	8.4 [7.4; 9.5]	7.4 [6.8; 8.2]	7.6 [6.9; 8.4]	**<.01**
BMI-SDS	0.59 [−0.13; 1.28]	0.75 [0.06; 1.33]	0.54 [−0.10; 1.24]	**<.01**
Pump use (%)	45.4	40.0	39.1	n.s.
DKA on follow-up (%)	3.5	1.3	1.8	n.s.
SH on follow-up (%)	3.9	1.5	3.4	n.s.

[a]Descriptive data were summarized using median [Q1;Q3] for continuous variables or proportion (%) for binary variables. A two-sided *P* value < .05 was defined as statistically significant.
Abbreviations: n.s., not significant.

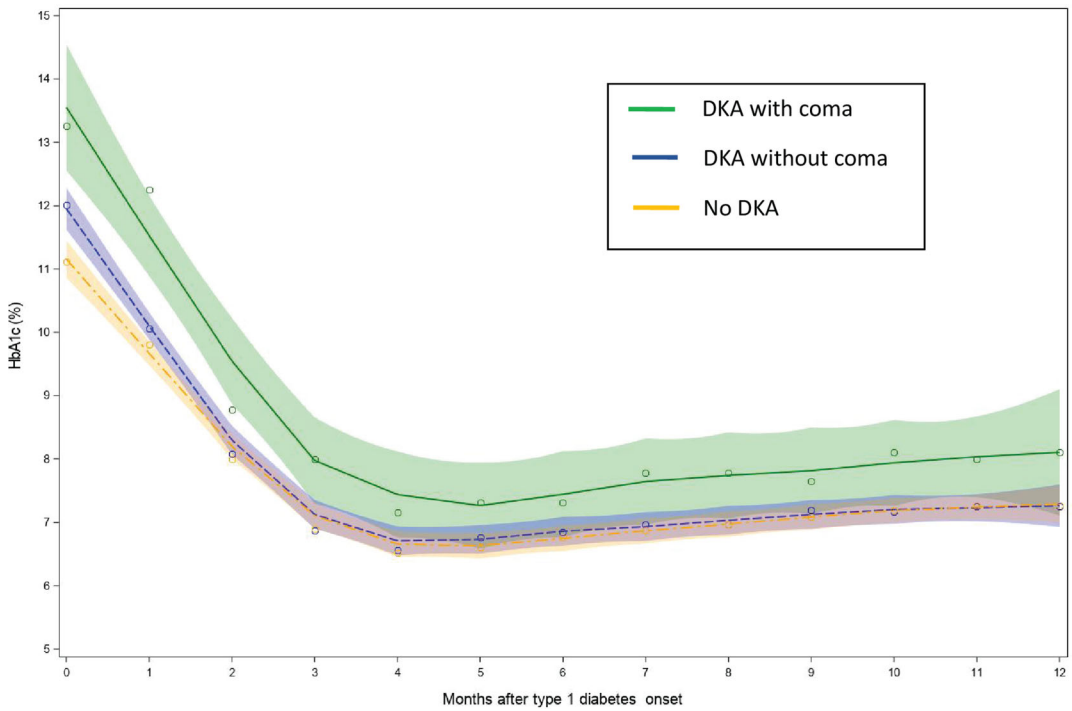

FIGURE 1 HbA1c (%) by month during the first year after T1D diagnosis in each presentation at onset group. Curves of HbA1c per month were estimated using locally weighted scatterplot smoothing (LOESS). Line and shaded area: Loess fit and 95% CI

(*P* < .01) (Table 2). Even after adjustment for demographics (Table S1) and additional adjustment for pump use similar results were found. After further adjustment for BMI-SDS and daily insulin dose, similar results were detected.

3.3.2 | Association of age groups-year-three HbA1c

Year-three HbA1c, adjusted for gender and region, was evaluated among the three age-groups (Figure **S2**). In the youngest age group

(<6 years), HbA1c was higher in the *DKA with coma* group than in the *DKA without coma* and *no DKA* groups (both $P < .01$). In children aged 6 to <12 years at onset, higher HbA1c was found in the *DKA with coma* group compared to the *DKA without coma* group ($P < .01$). No significant difference was observed for the 12 to 18 years age group at onset.

3.3.3 | Association of region-year-three HbA1c

Year-three HbA1c, adjusted for age at onset and gender among each region (Figure S3), was studied in order to compare year-three HbA1c among presentation at onset groups in each region separately. In Northern Europe, year-three HbA1c was better in children who experienced *DKA with coma* compared to children with *DKA without coma* and with *no DKA* (both $P < .01$). At the opposite, in America and Canada, the highest year-three HbA1c was reached by children who had *DKA with coma* compared to children with *DKA without coma* ($P < .01$) and with *no DKA* ($P < .01$). In children from Southern Europe and from Australia/New Zealand, no significant differences were found.

Pump use was 27% of children during the first year, increasing to 40% during the third year (Table 1), without differences among the presentation at onset groups (Table 2), even after adjustment for demographics (Table S1).

BMI-SDS during the third year was higher in patients who presented *DKA without coma* at T1D onset compared to subjects with *no DKA* ($P < .01$) (Table 2) and this difference was maintained after adjusting for demographics (Table S1).

The frequency of acute complications was low during the third year: DKA was observed in 2% of children and SH in 3%, without significant differences among the three presentation at onset groups (Table 2). However, when results were adjusted for demographics, SH was lower among the *DKA without coma* group compared to the *DKA with coma* and *no DKA* groups (Table S1).

3.4 | Sub-analysis: Sub-cohort with documented HbA1c at onset

In the sub-cohort of subjects with documented HbA1c at onset, 1420 subjects (54% male) were analyzed, including 994 from Northern Europe, 341 from Southern Europe, and 85 from America/Canada. Subjects with documented HbA1c at onset and the entire study cohort were clinically similar. In the sub-cohort, 6% of children presented *DKA with coma* at T1D manifestation, 37% *DKA without coma* and 57% presented *no DKA*.

3.4.1 | Analyzing presentation at onset groups

All results are adjusted for demographics and regions. HbA1c at onset was similar in children experiencing *DKA with coma* (HbA1c 12.2% [11.7;12.7]) and *DKA without coma* (HbA1c 12.1% [11.9;12.3]), while in children with *no DKA* lower HbA1c at onset was found (HbA1c 11.2% [11;11.4], $P < .01$).

No relevant differences were found in year-three HbA1c among the three presentations at onset groups (Figure 2A). Similar results were found when adjusted for HbA1c at onset and even when additionally adjusted for pump use.

3.4.2 | Analyzing HbA1c at onset groups: low HbA1c < 10% (<86 mmol/mol); medium HbA1c 10-<12% (86-<108 mmol/mol); high HbA1c ≥ 12% (≥108 mmol/mol)

All results are adjusted for demographics and regions. Year-three HbA1c was lower (7.4% [7.3;7.5]) in *low* HbA1c at onset group

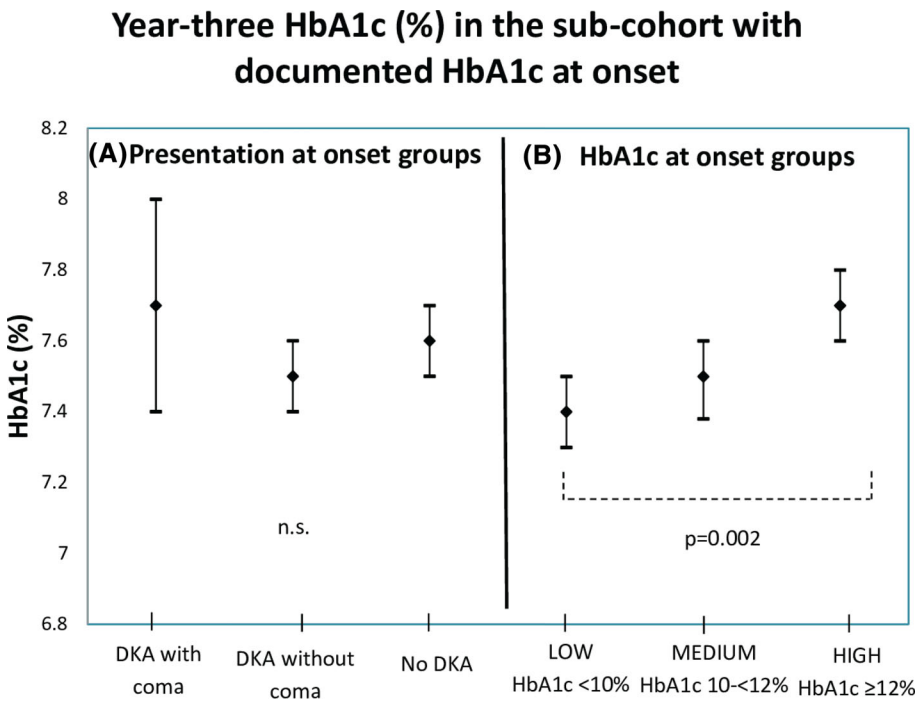

FIGURE 2 Year-three HbA1c (%) in the sub-cohort with documented HbA1c at onset, among presentation at onset, A, and HbA1c at onset groups, B, adjusted for age at onset, gender, and region. n.s. = not significant. Linear regression models adjusted for age at onset, gender and region were applied. A two-sided *P*-value '0.05 was defined as statistically significant

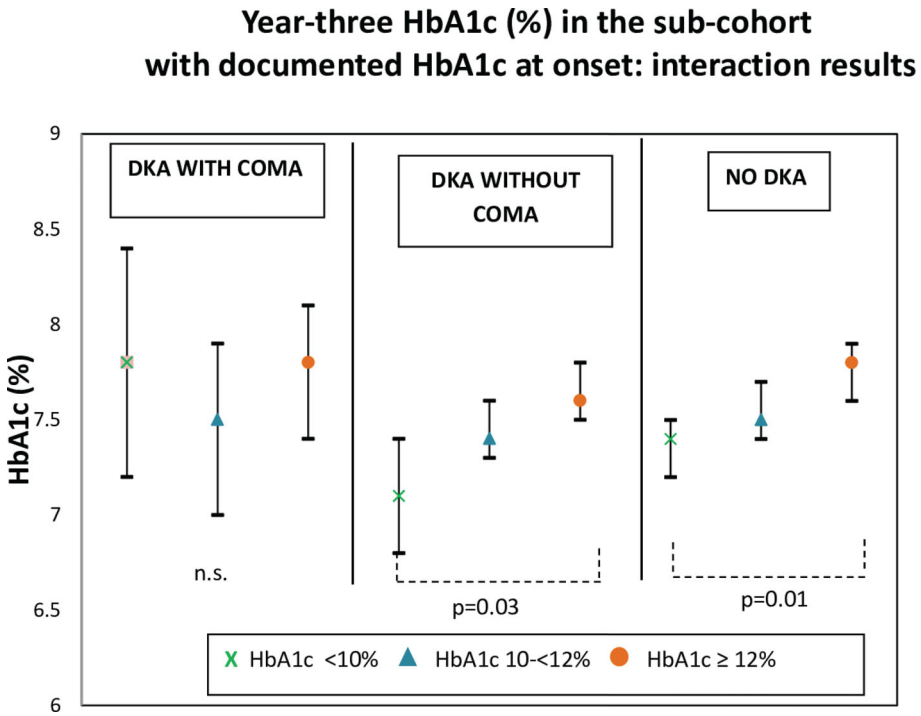

FIGURE 3 Results of the interaction between presentation at onset and HbA1c at onset model in the sub-cohort with documented HbA1c at onset, adjusted for age at onset, gender, and region. Linear regression model with interaction term presentation at onset group and HbA1c at onset group adjusted for age at onset, gender and region was applied. A two-sided *P*-value '0.05 was defined as statistically significant

compared to *high* HbA1c at onset group (7.7% [7.6;7.8], $P < .01$). No differences in metabolic control during the third year were detected between children in *medium* HbA1c at onset group (7.5% [7.4;7.6]) and both groups *high* or *low* HbA1c at onset (Figure 2B). Even after adjustment for pump treatment, we recognized the same association.

3.4.3 | Interaction between presentation and HbA1c at onset groups

Year-three HbA1c was lower in the *low* HbA1c at onset group compared to *high* HbA1c at onset group both in the *DKA without coma* group ($P = .03$) and in the *no DKA* group ($P = .01$), without differences between *low* and *medium* HbA1c at onset groups (Figure 3). No significant differences in year-three HbA1c were identified among the *DKA with coma* group ($P = 1$). Results were adjusted for regions, age at onset and gender.

Comparing the models HbA1c at onset groups versus presentation at onset groups, HbA1c at onset as explanatory variable was closer to the true distribution of the year-three HbA1c data (vuong test, $P = .02$), showing a closer association between HbA1c at onset groups and year-three HbA1c than between presentation at onset groups and year-three HbA1c.

4 | DISCUSSION

The international, multicenter SWEET registry provided the first and unique opportunity to investigate the association between DKA at onset, HbA1c at onset and 3 years metabolic control in a heterogeneous, multinational cohort of children with T1D. In the full study cohort, we found that more than half of the children were diagnosed without DKA at onset, but the proportion of children with DKA at onset (43%) is still too high worldwide, suggesting that T1D is not diagnosed early enough and in particular we observed an impressively high rate of *DKA with coma* (16%). Children who experienced *DKA with coma* at diagnosis presented with the highest HbA1c during the first year after diagnosis and highest year-three HbA1c, compared to children with *DKA without coma* and *no DKA*. Similar results were found after adjustment for demographics and neither pump use modulated year-three HbA1c. Thus, we could speculate that *DKA with coma* is related to higher year-three HbA1c, but analyzing the subcohort of patients with both presentation at onset and HbA1c at onset documented, we detected that year-three HbA1c was not significantly different based on T1D presentation. On the other hand, looking at the interaction between HbA1c and presentation at onset groups, we found that year-three HbA1c is more closely related to the levels of HbA1c at onset and therefore to chronic, sustained hyperglycemia and long-term glycemic trend and fluctuations, than to the different T1D presentation. This is particularly true in case of *DKA without coma* and *no DKA* at T1D onset. The presence of *DKA with coma* itself seems to be independently related to a higher year-three HbA1c since it could be a clue of long-lasting hyperglycemia and severe insulin deficiency, not promptly recognized. The clinical presence of coma is associated with a delay of diagnosis and therefore of treatment and thus with a sustained and durable hyperglycemia and moreover it is usually associated with a severe acidosis, even if pH at T1D onset is not a documented parameter in the SWEET dataset. Our results do not support the hypothesis that the presence of DKA at onset could act as a spring resulting in better long-term metabolic control, as it frightens families and they pay more attention to their diabetes. An exception was observed in Northern Europe, where the

lowest year-three HbA1c was found in the *DKA with coma* group. This could be related to the low prevalence of coma at T1D onset and a more intensive insulin treatment and education in these countries.

In the United States, 30% to 46% of children newly diagnosed with T1D experience DKA, one third severe DKA (pH <7.1). Moreover, a persistent negative correlation between DKA at diagnosis and glycemic control was described previously.[16] Duca et al (2017) showed how HbA1c in children with severe DKA at onset tracked 1.4% higher than children without DKA, independently of demographic and socioeconomic factors.[16] The study based on DanDiabKids (2013) showed that DKA was present at T1D manifestation in 17.9% of children and that 9.6% of children had moderate-severe DKA, which was associated with poor long term metabolic control.[13] Recently, Shalitin et al (2018) showed that DKA at diagnosis was present in 39.3% of patients and was associated with less favorable long-term glycemic control, as assessed by HbA1c and the rate of subsequent DKA episodes.[31]

In this study, we did not find any significant difference in the distribution of DKA in the three age groups, even if some studies report DKA at onset is more common in younger children, due to delayed symptoms recognition. Cherubini et al (2016) reported that in Italy 50% of children under 5 years and 60.7% under 2 years of age had DKA at diagnosis,[15] which is in line with data from the DanDiabKids registry.[13] In the present study cohort, younger children (<6 years) with *DKA with coma* at onset had worse third-year HbA1c compared to both children with *DKA without coma* and *no DKA*. Interestingly, children with age at onset ≥12 years showed the worst metabolic control regardless the type of presentation at onset, maybe due to the challenge of diabetes management during adolescence.

Considering year-three HbA1c among different regions, in Northern Europe a better HbA1c was achieved in children with *DKA with coma* at onset, compared to children with *DKA without coma* and with *no DKA*. At the opposite, in America and Canada, the worst metabolic control was detected in children who experienced *DKA with coma*. It could be speculated that the high T1D incidence and awareness in North European countries[1] are responsible for the low frequency of presentation with DKA and coma confirmed in this study and the small number of patients with DKA at onset could make it easier to fine-tune tailored intensive insulin therapy and develop continuous education. On the other hand, in America/Canada, the difference in year-three HbA1c among the three presentation at onset groups is largest and inverse compared to Northern Europe. These results could be explained by the fact that in rural areas in America/Canada patients must travel long distance to the nearest hospital and that the rural areas are very dependent on urban areas for health care.[32] Fox et al (2018) recently reported that children traveling more than 2 hours to attend a tertiary T1D clinic had significantly higher mean HbA1c.[33] Younger age, ethnic minority, lower family income and lack of health insurance were identified as major risk factors for DKA at T1D onset.[14] Thus, social and ethic differences could justify higher rate of DKA at onset and worse year-three Hba1c in America/Canada.

The Pediatric Diabetes Consortium T1D new onset (Neon) study assessed clinical outcomes in 857 children treated at seven US diabetes center from the time of diagnosis (33% DKA).[34] HbA1c gradually increased in all groups, in line with what we observed in the present study, with worse metabolic control in children with *DKA with coma* at onset. The concept of "metabolic tracking" highlights the importance of striving for optimal control soon after T1D diagnosis, which may lead to better control in the long term.[19,20] Our study suggests that "metabolic tracking" could start very early, even before T1D diagnosis, from the very beginning of chronic hyperglycemia, recognizing a closer association between HbA1c at onset and year-three HbA1c, compared to the presence of DKA at onset and confirming that year-three HbA1c is higher in children with HbA1c ≥ 12% at T1D onset. The importance of HbA1c at disease onset is not well-known and current studies either include few patients or have short follow-up time and none is based on multicenter, international data. Some authors highlighted the role of metabolic memory, suggesting that pre-diagnosis exposure to elevated glucose levels has a bearing on subsequent outcome.[35,36] Future research is needed to establish why children with high HbA1c values at diagnosis continue to have worse metabolic control and if this is related to pathophysiological or genetic issues. Our results on the relationship between clinical presentation at onset and later metabolic control are based on a biological model. However psycho-social/family factors might also be a reason for delayed diagnosis (and presentation with DKA) and have an impact on future care, resulting in higher HbA1c values. Future studies should focus on this alternative model in order to understand the impact of education and social support, and, on the other hand, of advanced technology and intensive education.

The current study has inherent strengths and limitations. The main strengths of the study are the large sample size, the highly heterogeneous, international population, a worldwide dataset and the SWEET data quality control. One limitation of the present study might be that HbA1c was not measured in a central laboratory, however, to reduce variation between laboratories, HbA1c levels were mathematically standardized. Moreover,T1D onset data is not complete enough in the SWEET dataset and HbA1c at onset was available for 48% of children and therefore some selection bias cannot be excluded. Some socioeconomic and demographic factors have not been considered in the study because they are not available in the SWEET database. Treatment at T1D onset could be different between centers and countries and also the hospitalization length and the level of initial education provided by nurses, dietitians and pediatric diabetologists could vary. We did not take into account how intensive were the initial T1D treatment and education.

In conclusion, in this heterogeneous, multinational cohort of children considered year-three HbA1c was more closely associated with HbA1c at onset compared to clinical presentation (DKA) at onset. While children who experienced DKA at onset can achieve a good metabolic control, patients with *high* HbA1c at onset continue to have poor metabolic control as a group. Coma itself is also associated with subsequent poor metabolic control. These results emphasize the importance of identifying from the very beginning of T1D a subset of children (eg, those with HbA1c at onset ≥12% and those with DKA and coma, especially if younger) at major risk of future poor metabolic

control, in order to implement intensive education and recent technological advances. Early detection of T1D, preventing a high HbA1c at onset as well as DKA at onset with coma, is crucial to improving year-three HbA1c.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

B.P. wrote the first draft of the manuscript. B.P. and A.S. researched data and reviewed/edited the manuscript. A.S. analyzed the data. The remaining authors collected center data, uploaded, and validated data to SWEET. All authors discussed the results, edited on drafts and approved the final manuscript.

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SUPPORTING INFORMATION

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