ORIGINAL ARTICLE

Effect of ultra-rapid insulin aspart on glycemic control in children with type 1 diabetes: the experience of a Portuguese tertiary centre

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Abstract

Background Postprandial hyperglycemia is one of the biggest challenges in children with type 1 diabetes (T1D). Ultra-fast-acting aspartic insulin (faster aspart) has a quicker onset of action and an earlier maximum activity. The aim of this study is to analyze the impact of faster aspart in metabolic control of pediatric patients with T1D in a "real-world" setting.

Methods Retrospective analysis of 60 pediatric patients with T1D who changed their insulin analogue to faster aspart. Anthropometric data, insulin doses, capillary and interstitial glucose recordings and average glycated hemoglobin before and after insulin analogue's switch were obtained. After all population analyses, patients were analyzed separately according to the type of treatment, multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), and according to age group.

Results Faster aspart significantly improved metabolic control, increasing time in range (TIR) (42 vs.54%, respectively; $P = 0.007$) and decreasing time above range (TAR) (52 vs.40%, respectively; $P = 0.009$), without an increased time in hypo-glycemia (7% before and after faster aspart's introduction; $P = 0.933$). This was reassured in the adolescent years ($n = 45$), with an increase in TIR (37 vs. 47%, respectively; $P = 0.034$) and decrease in TAR (51 vs. 45%, respectively; $P = 0.022$). Patients on CSII ($n = 47$), also demonstrated an increase in TIR (38 vs. 50%, respectively; $P = 0.010$). The reduction of A1c was not statistically significant.

Conclusion Although the advantage of faster aspart had already been demonstrated in pediatric patients under MDI, "real-world" studies, including patients under CSII, are still lacking. This study highlights the important impact of faster aspart on metabolic control in children with T1D, particularly among adolescents under CSII.

Keywords Pediatric age · Type 1 diabetes · Fast aspart insulin

Introduction

Postprandial glucose variations are a major problem in type 1 diabetes (T1D) control, as they cause glucose toxicity and accelerate the progression of diabetic complications, being considered an independent risk factor for macrovascular disease [1]. This is even more relevant in pediatric population, given their hopefully longer life expectancy.

The recognition of deleterious effects from the exposure to long-time hyperglycemia, shows the importance of an intensive treatment starting at diagnosis and during the whole life. The concept of metabolic memory [2–5], or the cumulative glycemic exposure as recently proposed by *Miller* and *Orchad* [5], and the disseminated access to continuous glucose monitoring, promoted the aim of longer time in target with the lowest variability [6]. Along with higher rate of long-term micro/macrovascular complications, hyperglycemia has also been proven to affect negatively cognitive function and academic performance [7, 8].

Despite pharmacological and technological advances in diabetes, currently available rapid-acting insulin analogues

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are still not able to mimic a human pancreas. Their onset of action is slower than endogenous insulin and their duration is longer than desired. Evidence shows that delivering a bolus 15–20 min before eating rather than immediately before or after the meal improves significantly postprandial glycemic control [9, 10]. If a child is hyperglycemic at mealtime, the waiting time should be even longer to avoid postprandial spikes, which can be challenging in pediatric population. Parents can be reluctant to administer insulin before a meal, particularly in younger children and in the context of acute diseases, due to the propension to hypoglycemia if the child does not eat what was previously estimated [11]. On the other hand, as older children and adolescents are developing autonomy to manage diabetes treatment, spending less time under parental surveillance, the waiting time before a meal can be difficult to accomplish in daily life.

The widespread use of glucose monitoring systems enabled the access to glycemia excursions along all day, including the peak of postprandial hyperglycemia and glycemic variability, and emphasized the need to control it [12, 13].

Ultra-fast-acting insulin aspart (faster aspart), Fiasp®, is composed of aspartic insulin with two additional excipients: l-arginine which acts as a stabilizing agent and niacinamide which promotes accelerated initial absorption after administration of the drug. Both excipients contribute to a more stable formulation and faster initial absorption after subcutaneous injection [14, 15]. These theoretical pharmacokinetic and pharmacodynamic advantages have been proven in several clinical studies [16–18]: faster aspart demonstrated to reduce postprandial glucose (PPG) in all studies with an associated positive impact on glycosylated hemoglobin (A1c) in patients under multiple daily injections (MDI).

Nevertheless, real-life studies evolving children and adolescents are still lacking. The purpose of this study is to assess the impact of changing the rapid-acting insulin analogue to Fiasp® in children and adolescents with T1D under basal-bolus regimen in a "real-world" setting.

Aim

We intended to analyze the effect of ultra-rapid insulin analogue on the metabolic control of children and adolescents with type 1 diabetes.

Methods

Research design

This was a retrospective study including children and adolescents with T1D, all under basal-boluses regimen and with disease duration of at least two years, who started with an ultra-rapid insulin analogue (faster aspart) at least 3 months

before. Data were acquired from the clinical records of follow-up appointments in Coimbra's Pediatric Hospital, a Portuguese tertiary referral center, from September 2019 to November 2020. We highlight the fact that this period included the beginning of COVID-19 pandemic and the most rigorous period of confinement in Portugal.

Patient selection

Of the 253 children and adolescents with diabetes followed in this period, we selected 131 patients, who were under faster aspart. We excluded 71 cases: 50 who changed the type of treatment during the study, 18 that had shorter treatment duration, 2 who were treated with Fiasp® since diabetes' diagnosis and 1 with a post-pancreatectomy diabetes (Fig. 1). The 60 patients, under MDI or continuous subcutaneous insulin infusion (CSII) before and after the treatment, respectively, were included in the study. Six patients (10%) were using a predictive low-glucose management (PGLM) system under MiniMed™ 640G, while the remaining 54 patients (90%) were using MiniMed Paradigm® Veo, ACCU-CHEK Spirit Combo® or MiniMed™ 640G with self-monitoring of blood glucose (SMBG) and/or interstitial glucose monitoring. Those treated with MDI were maintained under the same long action insulin analogue.

Methodology

Our primary aim was to assess the effect of switching the rapid-acting insulin analogue to faster aspart on glycemic control of children and adolescents with T1D, comparing the following parameters before and after the introduction of the ultra-rapid analogue: capillary and interstitial glucose recordings, % of time in range (TIR), % of time above range
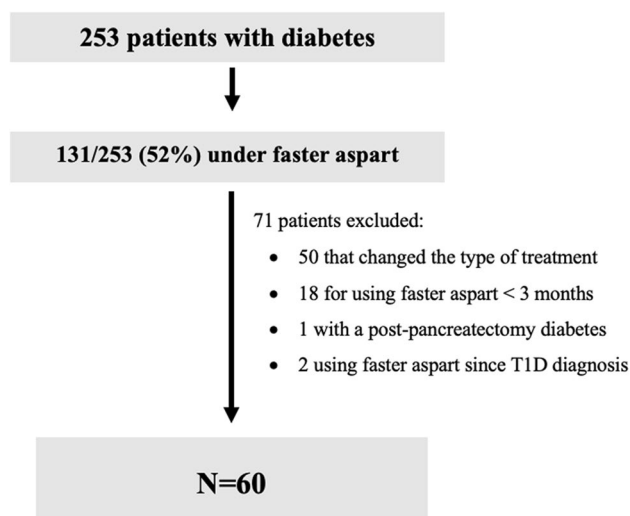

Fig. 1 Selection of patients included in the study

(TAR) and % of time below range (TBR), glucose variability coefficient and A1c.

Interstitial continuous (CGM) and intermittent (Freestyle Libre®) glucose monitoring systems were used, and target was defined as 70–180 mg/dL. TBR and TAR was described as the percentage of time below 70 mg/dL and above 180 mg/dL, respectively, as recommended by the international consensus of 2019 [6]. Data obtained were referred to the 14 days prior to the appointment with an average data capture of 70%. SMBG was done using bolus calculator meters.

Secondary aim was to evaluate the impact of this insulin switch on daily insulin requirements and body mass index (BMI). Anthropometric data (weight, height, BMI), insulin daily doses (including % of basal and bolus) were collected from the last medical appointment under the previous insulin analogue and compared to data collected from the most recent follow-up, under the faster aspart insulin. Using the Z-score distribution of each anthropometric indicator, the standard deviation (SD) of each measure was calculated. The average A1c was calculated by the mean of all values in the year before and after the insulin switch. C-peptide value (ng/ml) was collected from the annual laboratorial evaluation before insulin switch.

After the analysis of total population ($n = 60$), a subgroup analysis was performed according to the type of treatment—MDI or CSII—and the age group—children (from 3 to 10 years old, exclusively) and adolescents (from 10 to 19 years old, inclusively). The glycemic control before and after switching to faster aspart was evaluated in each of the groups. The definition of children and adolescents was based on World Health Organization (WHO).

Statistical analysis

Quantitative variables were assessed for normality with Shapiro–Wilk tests and graphical assessment. Quantitative variables were described in terms of their mean standard deviation, in which median values, as well as their first and third quartiles were used. Nominal variables were, in turn, described by absolute and relative frequencies. Quantitative variables were compared between two points in time (before and after insulin switch) resorting to Wilcoxon or Paired sample t test, where appropriated. Statistical significance was defined as $P < 0.05$ (two-tailed) and SPSSv25 was used.

Results

Of the 60 children and adolescents selected, 53% ($n = 32$) were males with an average age of 12.3 ± 4.1 years. The patients had T1D for about 6.1 ± 3.6 years and were under faster aspart for 5.7 ± 2.5 months. Around 89% ($n = 47$) of patients were using interstitial glucose monitoring, among these 87% ($n = 41$) with an intermittent and 13% ($n = 6$) with a continuous system.

Patients under CSII ($N = 47$) presented with longer disease duration and higher daily insulin requirements comparing to MDI-treated patients ($N = 13$) (6.0 vs 3.1 years, respectively; $P = 0.027$ and 0.94 vs 0.69 U/kg/day, $P = 0.044$). However, no statistically significant differences were found on C-peptide or A1c levels between groups (Table 1).

Total population ($n = 60$)

With the insulin switch to faster aspart, there was a statistically significant increase in TIR (42 vs. 53%, respectively; $P = 0.007$) in interstitial glucose monitoring and a significant decrease in TAR (52 vs. 40%, respectively; $P = 0.009$), without an increasing TBR (7 vs. 7%, respectively; $P = 0.933$) (Table 2). These results did not have a statistically significant impact on A1c (7.7% before and 7.6% after faster aspart; $P = 0.529$).

Concerning to insulin doses, total daily doses were stable during the study (0.99 vs. 0.98U/kg/day pre and post faster aspart, respectively; $P = 0.759$) as well as basal/boluses

Table 1 Comparison between patients under MDI and patients under CSII

	MDI (aspart → faster aspart) N = 13	CSII (aspart → faster aspart) N = 47	P value
Age (years)	12.3 (9.1;16.1)	12.8 (10,6;16.2)	0.693
T1D duration (years)	3.1 (1.2;4.7)	6.0 (4.5;9.8)	**0.027**
C-Peptide (ng/mL)	0.5 (0;0.6)	0.1 (0;0.5)	0.405
TDD (U/kg/day)	0.69 (0.58;0.86)	0.94 (0.75;1.22)	**0.044**
Average A1c (%)	7.4 (6.6;7.7)	7.8 (7.3;8.4)	0.051
	N = 60		

Bold text indicates a statistically significant difference ($P < 0.05$)

MDI Multiple daily injections, *CSII* continuous subcutaneous insulin infusion, *A1c* glycated hemoglobin, *T1D* type 1 diabetes, *TDD* total daily dose

*The average A1c was calculated in the year before changing to faster aspart

Table 2 Comparison of anthropometric data, insulin doses, interstitial glucose recordings and A1c before and after changing the insulin analog to faster aspart (Fiasp®)

	Total population			CSII		
	N = 60			N = 47		
	Before faster aspart	After faster aspart	P	Before faster aspart	After faster aspart	P
Anthropometric data						
Weight (z-score)	0.86 ± 1.08	0.96 ± 0.94	0.430	0.73 ± 1.04	0.94 ± 0.93	0.147
Height (z-score)	0.16 ± 0.96	0.21 ± 0.95	0.280	0.11 ± 1.01	0.14 ± 0.99	0.537
BMI (z-score)	0.58 ± 0.99	0.64 ± 0.96	0.274	0.55 ± 1.01	0.63 ± 0.98	0.218
Insulin doses						
Bolus (U/day)	34.5 ± 25.2	34.3 ± 20.5	0.912	38.8 ± 26.2	36.6 ± 20.3	0.436
Bolus (U/Kg/day)	0.67 ± 0.33	0.64 ± 0.29	0.364	0.75 ± 0.31	0.70 ± 0.27	0.174
Bolus (%)	64 ± 13	63 ± 12	0.804	67 ± 11	66 ± 11	0.162
Basal (U/day)	16.2 ± 8.3	17.8 ± 8.9	**0.007**	16.3 ± 8.2	17.9 ± 8.4	**0.025**
Basal (U/Kg/day)	0.31 ± 0.10	0.32 ± 0.13	0.378	0.31 ± 0.10	0.33 ± 0.12	0.477
Basal (%)	36 ± 13	37 ± 11	0.466	32 ± 10	34 ± 10	0.067
Total (U/Kg/day)	0.99 ± 0.35	0.98 ± 0.32	0.759	1.07 ± 0.33	1.03 ± 0.30	0.338
Flash glucose monitoring						
Mean glucose (mg/dL)	194 ± 31	178 ± 31	**0.030**	192 ± 33	179 ± 25	0.059
Time in range (%)	42 ± 18	53 ± 14	**0.007**	38 ± 16	50 ± 13	**0.010**
Time above range (%)	52 ± 20	40 ± 16	**0.009**	55 ± 21	43 ± 15	**0.017**
Time below range (%)	7 ± 4	7 ± 5	0.933	7 ± 4	7 ± 6	0.894
A1c (%)*	7.7 ± 0.9	7.6 ± 0.9	0.529	7.8 ± 0.8	7.6 ± 0.8	0.070
Capillary blood glucose						
Mean glucose (mg/dL)	184 ± 33	188 ± 32	0.508	189 ± 36	195 ± 30	0.465
SD (mg/dL)	84 ± 17	79 ± 15	0.138	88 ± 13	81 ± 14	0.151
CV (%)	46 ± 8	42 ± 7	0.145	46 ± 7	42 ± 7	0.174
Values in range (%)	38 ± 11	36 ± 17	0.796	41 ± 6	32 ± 19	0.500
Values above range (%)	54 ± 10	57 ± 21	0.718	57 ± 6	65 ± 18	0.500
Values below range (%)	8 ± 7	7 ± 7	0.528	3 ± 0	4 ± 1	0.500

Bold text indicates a statistically significant difference (P < 0.05)

MDI Multiple daily injections, *CSII* continuous subcutaneous insulin infusion, *A1c* glycated hemoglobin, *SD* standard deviation, *CV* coefficient of variation

*The average A1c was calculated in the year before changing to faster aspart and in the year after changing

proportions (basal 36 vs. 37%, respectively; P = 0.466; bolus 64 vs. 63%, respectively; P = 0.804). There was an increase in absolute values of basal insulin (16.2 vs. 17.8 U/day; P = 0.007), explained by growth and weight gain characteristic of this age group, that was not observed when basal insulin was adjusted to the weight (0.31 vs. 0.32 U/Kg/day before and after the switch to faster aspart; P = 0.378).

As for anthropometric data, there was no increase in BMI after switching to faster aspart (0.58 vs. 0.64 SD, respectively; P = 0.274).

Sub-analysis according to type of treatment

In the CSII group (N = 47), it was confirmed a significant increase in TIR with faster aspart's (38 vs. 50%, respectively; P = 0.010) and a decreased TAR (55% before

and 43% after the switch to faster aspart, respectively; P = 0.017), without change in TBR (7 vs 7%, P = 0.894). Although not statistically significant, there was also a decline in mean interstitial glucose (192 vs 179 mg/dL, respectively; P = 0.059) and A1c (7.8 vs 7.6% post faster aspart's introduction; P = 0.07).

There was no change in insulin daily doses during the study (basal insulin 0.31 vs. 0.33 U/kg/day, P = 0.477; bolus insulin 0.75 vs. 0.70 U/kg/day; P = 0.174), and insulin proportions also remained constant. No statistically significant changes in anthropometric data were found (Table 2).

There was a small group of T1D patients under MDI (N = 13) and we found no significant differences regarding any of the variables studied, before and after switching to faster aspart.

Sub-analysis according to age groups

In younger T1D patients, defined here as children's group (N = 15), switching to faster aspart insulin did not change significantly metabolic control. However, there was a trend towards an improvement in TIR (45 vs. 58% before and after, respectively; P = 0.068) and a decrease in TAR (49 vs. 32%, respectively; P = 0.068), as well as a decrease in mean glucose (192 mg/dL vs 179 mg/dL, respectively; P = 0.075). TBR remained constant (4 vs. 4%, P = 0.446). Total daily insulin and basal and bolus proportions remained stable (Table 3). Only absolute values showed a tendency to increase bolus units (11.5U/day vs. 15.4U/day; P = 0.046) and decrease basal units (6.8U/day vs. 6.7U/day; P = 0.046), reflecting the increasing carb ingestion during this age and the consequent need to adjust basal insulin. When adjusted for body weight, there were no statistically significant changes in any of these variables, including bolus (0.5U/Kg/day of before and after faster aspart; P = 0.414) and basal (0.2U/Kg/day of before and 0.3U/Kg/day after faster aspart; P = 0.414) insulin doses.

In the adolescents' group (N = 45), there was a significant increase in TIR with faster aspart (37 vs. 47%, respectively before and after switch; P = 0.034), with a consequent decrease in TAR (51 vs. 45%, respectively; P = 0.022). TBR remained stable (7 vs. 6%, before and after the switch, respectively; P = 0.776), as well as A1c (7.7 vs. 7.7%, before and after the switch; P = 0.266). Insulin doses and capillary glucose measurements did not undergo statistically significant changes with the modification of insulin analog (Table 3).

Discussion

This "real-world" uni-centric study performed in a pediatric population confirmed that switching to faster aspart improves metabolic control, it is safe in pediatric population and compatible with different types of treatment.

The results of ONSET trials [16–18] have been supported by several "real-world" studies in adults [19, 20]; however, studies in pediatric population are still lacking. Comparing with adults' trials, the 11% increase in TIR observed in our

Table 3 Comparison of insulin doses, interstitial glucose recordings and A1c before and after changing the insulin analog to faster aspart (Fiasp®) according to age group

	Children			Adolescents		
	N = 15			N = 45		
	Before faster aspart	After faster aspart	P	Before faster aspart	After faster aspart	P
Insulin doses						
Bolus (U)	11.5 (7.0;18.3)	15.4 (9.8;22.9)	**0.046**	27.6 (22.0;50.2)	36.7 (24.5;51.4)	0.961
Bolus (U/Kg/day)	0.5 (0.3;0.6)	0.5 (0.4;0.8)	0.414	0.6 (0.4;0.8)	0.6 (0.4;0.9)	0.343
Bolus (%)	62 (53;70)	64 (60;69)	0.917	65 (50;73)	65 (53; 74)	0.783
Basal (U)	6.8 (4.4;8.3)	6.7 (4.7;11.5)	**0.046**	17.7 (12.0;24.0)	17.9 (14.4;24.1)	**0.002**
Basal (U/Kg/day)	0.2 (0.2;0.4)	0.3 (0.2;0.4)	0.414	0.3 (0.3;0.4)	0.3 (0.3;0.4)	0.660
Basal (%)	35 (25;46)	37 (32;40)	0.753	37 (27; 46)	35.0 (26;47)	0.685
Total (U/Kg/day)	0.76 (0.64;0.98)	0.87 (0.60;1.06)	0.779	0.93 (0.70; 1.27)	1.00 (0.85; 1.20)	0.503
Flash glucose monitoring						
Mean glucose (mg/dL)	192 (162; 210)	179 (159; 186)	0.075	184 (161; 203)	177 (159; 204)	0.094
Time in range (%)	45 (31; 55)	58 (45; 64)	0.068	37 (21; 51)	47 (39; 58)	**0.034**
Time above range (%)	49 (37; 67)	35 (32; 51)	0.068	51 (37; 76)	45 (30; 56)	**0.022**
Time below range (%)	4 (1; 9)	4 (4; 5)	0.461	7 (4; 12)	6 (4; 8)	0.776
A1c (%)*	7.4 (7.1;7.8)	7.3 (7.1;7.9)	0.859	7.70 (7.30; 8.40)	7.70 (7.10; 8.40)	0.266
Capillary blood glucose						
Mean glucose (mg/dL)	165 ± 7	173 (153;215)	0.173	197 (164;217)	179 (164;218)	0.586
SD (mg/dL)	91 (76;95)	75 (57;81)	0.273	86 (68;97)	80 (70;95)	0.278
CV (%)	49 (45;53)	42 (37;52)	0.180	45 (36;52)	43 (38;48)	0.346
Values in range (%)	28 (28;41)	32 (7;47)	0.655	34 (24;43)	32 (19;41)	0.180

Bold text indicates a statistically significant difference (P < 0.05)

MDI Multiple daily injections, *CSII* continuous subcutaneous insulin infusion, *A1c* glycated hemoglobin, *SD* standard deviation, *CV* coefficient of variation

*The average A1c was calculated in the year before changing to faster aspart and in the year after changing

study was considerably higher, 3.2% [19] and 4% [20]. Similarly, we had a 12% decrease in TAR, also superior to what was found on both studies (3% [19] and 4.6% [20]). Nevertheless, A1c did not improve significantly, which is aligned with some [17, 20], but not all studies [16, 18, 19]. Besides the fact that the study was carried out in a population with a reasonably good metabolic control (Table 1), comparing the average of A1c with the previous year of faster aspart's introduction may have been a limitation. In fact, our study was carried out during the most rigorous period of confinement due to the COVID-19 pandemic in Portugal. Hence, although they could already demonstrate some deterioration in interstitial glycemic control at the beginning of our study, it is understandable that the mean A1c was not much higher. Furthermore, despite ONSET 7 [18] demonstrated a significant improvement of A1c with the switch to mealtime faster aspart, the study was performed in a pediatric population under MDI which does not match our population. Most of our patients were under CSII and the study performed in CSII-treated adult patients [17] did not show an improvement in A1C with faster aspart. In fact, we observed an improvement in the mean A1c (7.8% and 7.6%, before and after faster aspart) in patients under CSII, although without statistical significance ($P = 0.070$). However, this A1c decrease, points to a possible significant reduction in A1c in the future, considering a larger sample and longer follow-up time, and hopefully without daily life activity restrictions.

The analysis of patients under MDI throughout the study did not reveal statistically significant results probably due to its small sample size ($n = 13$). Additionally, as newly diagnosed patients in our unit start treatment with MDI and can only switch to CSII later on, depending on availability, those patients had a shorter disease duration (3.1 vs. 6 years) and they were better controlled (7.4 vs. 7.8%,) comparing to CSII-treated group (Table 1). Despite that, C-peptide levels were not significantly higher in the MDI group, which is probably related to the low number of assays available in an already small sample. All these circumstances together may have prevented the achievement of statistically significant results in this population.

Although PPG increments were not specifically evaluated in our study, considering these results, the pharmacokinetics of faster aspart [15] and the absence of an increase in time in hypoglycemia, we can infer that this improvement occurred essentially at mealtime. In addition to children's preference for carbohydrates with a high glycemic index, the lack of compliance regarding the "waiting time" between insulin administration and meal ingestion, is probably the most robust explanation for this improvement. In fact, when children and adolescents are analyzed separately, we found that the increase in TIR and the decrease in TAR remained statistically significant only in the older group. This reinforces the advantage of this insulin switch particularly in adolescents that tend to have less parental surveillance and are considered to have a lower treatment compliance. Notwithstanding, the number of children was considerably smaller compared to adolescents ($n = 15$ vs $n = 45$, respectively), which could also explain the absence of statistically significant results in the younger ones.

Concerning to insulin doses, total daily doses were stable during the study, as well as basal/boluses proportions. However, there was an increase in absolute values of basal insulin (16.2U/day vs. 17.8U/day; $P = 0.007$), explained by growth and weight gain characteristic of this age group. This difference was probably exacerbated by the period of confinement due to the pandemic COVID-19. Besides the suspension of all group sports, children and adolescents stopped going to school and started having classes at home, which may explain the increase in insulin needs due to the sedentary lifestyle.

In regard to anthropometric data, there was no increase in BMI after switching to faster aspart, even in this restrictive period.

We are aware that our research has some limitations, its retrospective design, the small number of patients included and its short follow-up time. As information was obtained from clinical records after medical appointments, we did not have access to all data, like post prandial glucose levels, which could have strengthened our study, as previously described [16–19].

Moreover, as this study involved the most rigorous period of confinement in Portugal, patients' lifestyle was inevitably altered and this was probably the main reason why there was a significant increase in absolute values of basal insulin during the study, which was not confirmed when the adjustment per kilogram of body weight was performed.

Nevertheless, it should be emphasized that some of this study limitations can also be seen as strengths. Given its retrospective and non-interventional nature, the decision to introduce faster aspart was exclusively based on the assistant physician's opinion and not with the aim of enrolling the patient in a study. Similarly, we can exclude that the improvement in glycemic control was due to the fact that patients were more compliant because of their participation in the study, since it was retrospective, and no changes were done in treatment education when faster aspart was introduced. Furthermore, we know that, particularly in the pediatric population, insulin boluses are not always administered before meals, either due to parents' fear or to adolescents' forgetfulness. Thereby, we cannot exclude that this may have happened in some of the cases and still there was an improvement in TIR and TAR.

Notwithstanding, in the future, it would be interesting to prospectively collect this data, with uniform parameters and longer follow-up duration, hopefully without any restrains to normal active life.

In summary, this "real-world" study reinforces that faster aspart improves metabolic control in T1D at pediatric age (increasing TIR and decreasing TAR), particularly in adolescents' challenging age, and in CSII-treated patients.

Author contributions CC, FB, MIL performed data acquisition. CC and JSC performed the research. CC performed statistical analysis and wrote the manuscript. JSC designed the research study, analyzed the data and made suggestions/corrections to the writing. All other authors (FB, MIL, RC, ID, MAM and APS) reviewed the article and provided fundamental theoretical and practical information. All authors have read and approved the final manuscript.

Declarations

Conflict of interest The authors declare no conflict of interest, including specific financial interests, relationships and affiliations that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study. The study protocol was approved by the Centro Hospitalar e Universitário de Coimbra's Ethics Committee on 15th July 2021 (approval number OBS.SF.57/2021).

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