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sciendo

144 ENDOCRINE REGULATIONS, Vol. 57, 144–151, 2023

doi:10.2478/enr-2023-0018

Efficacy and safety of SGLT2 inhibitors in individuals with type 1 diabetes under continuous subcutaneous insulin infusion: a real-world study

Vania Benido Silva, Liliana Fonseca, Diana Borges Duarte, Francisca Marques Puga, Guilherme Assuncao, Susana Garrido, Sofia Teixeira, Joana Vilaverde, Maria Helena Cardoso

Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitario do Porto, Porto, Portugal
E-mail: vania.benido@hotmail.com

Objective. Adjuvant therapy with sodium-glucose cotransport 2 inhibitors (SGLT2i) in type 1 diabetes (T1D) is associated with an improvement in glycemic control, but increases the risk of diabetic ketoacidosis (DKA). However, real-life studies in individuals with T1D under continuous subcutaneous insulin infusion (CSII) are still scarce. We present the first real-life study performed in patients with T1D exclusively treated with CSII. The aim of the present study was to assess the metabolic impact and safety of SGLT2i in T1D individuals under CSII.

Methods. Retrospective study includes 34 T1D adult individuals under CSII, who started SGLT2i until 30th June 2021. Data regarding the glycemic control and acute diabetes complications at the moment of introduction of SGLT2i and after 3, 6, and 12 months of use were collected.

Results. Twenty-three individuals were included. Comparing with the moment of SGLT2i introduction after 3, 6, and 12 months of use, there was a statistically significant increase of time in range (TIR) (Δ_{T3M}=12.8%; Δ_{T6M}=11.5%; Δ_{T12M}=11.1%), and a decrease in time above range (Δ_{T3M}=13.6%; Δ_{T6M}=11.9%; Δ_{T12M}=10.5%). There were no significant differences in time below the range. Mean glucose and mean glucose management indicator significantly reduced in the 3 evaluated moments. A significant reduction in median weight was also observed (Δ_{T6M}=2 kg; Δ_{T12M}=4.5 kg). Two patients (8.7%) developed mild euglycemic DKA during SGLT2i treatment, both were women and had body mass index (BMI) <27 kg/m^2. One of them had a total daily insulin dose (TDDI) reduction of 26.9% after 3 months of use.

Conclusions. The use of SGLT2i, as an adjuvant treatment in T1D individuals under CSII, was associated with a significant increase of TIR without increasing time in hypoglycemia. It also had a weight benefit. Careful use in selected participants is necessary to reduce the occurrence of DKA.

Key words: continuous subcutaneous insulin infusion, type 1 diabetes, sodium-glucose cotransport 2 inhibitors, diabetic ketoacidosis

Intensive insulin treatment remains the only option for effective management of type 1 diabetes (T1D), allowing for a strict glycemic control and a reduction in the risk of microvascular complications of diabetes (The DCCT Research Group 1988; Danne et al. 2019). However, despite the advances in diabetes technology over the last years, including new insulin formulations, introduction of continuous glucose monitoring systems (CGM), and advances in continuous subcutaneous insulin infusion devices (CSII), most individuals with T1D are not able to achieve the glycemic targets recommended by the American Diabetes Association (ADA) (Miller et al. 2015; Foster et al. 2019; ADA

Corresponding author: Vania Benido Silva, Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitario do Porto, Porto, Portugal; phone: +351913007447; e-mail: vania.benido@hotmail.com.

professional practice committee et al. 2022). Several adjunctive therapies have been explored in an effort to improve the metabolic control without increasing the risk of severe hypoglycemia or weight gain, two major barriers to the optimal use of insulin therapy (The DCCT Research Group 1988; DeGeeter and Williamson 2016; Danne et al. 2019).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are oral antidiabetic agents that act in the renal proximal tubule, reducing glucose and sodium reabsorption in an insulin-independent manner (DeFronzo et al. 2017). In individuals with type 2 diabetes (T2D), the metabolic and cardiorenal benefits are well established (Zinman et al. 2015; Wanner et al. 2016; Wiviott et al. 2019). Similarly, the adjunctive use of SGLT2i in individuals with T1D have been shown to improve glycemic control (including HbA1c and time in target range, TIR) without increasing time in hypoglycemia, as well as to reduce blood pressure, weight, and total daily insulin dose (TDDI) (Taylor et al. 2019). Furthermore, a *post hoc* analysis of DEPICT trials published in 2020 has suggested that this drug class also provides renal protection in people with T1D and albuminuria (Groop et al. 2020).

However, there have been many concerns regarding the use of SGLT2i in T1D. Due to the consequent reduction of TDDI and rise in the glucagon levels, an increase of lipolysis and ketogenesis can occur leading to an increased risk of ketonemia and diabetic ketoacidosis (DKA), often with lower glucose values than expected (euglycemic DKA) (Henry et al. 2015; Dandona et al. 2017, 2018; Mathieu et al. 2016, 2018). Individuals under CSII treatment are known to be even more susceptible to the development of these acute complications, due to the risk of catheter occlusion or pump system failure, but studies in this subgroup of people are scarce (Danne et al. 2019).

In this study, we aimed to assess the metabolic impact and safety of SGLT2i in T1D individuals under CSII.

Subjects and Methods

Subjects. A retrospective, longitudinal, clinical and observational study was conducted including all individuals with T1D treated with CSII and under SGLT2i at the Diabetes Outpatient Clinic of Centro Hospitalar Universitario do Porto, a tertiary and academic hospital in Portugal. This study was approved by our Institutional Review Board and our Institutional Ethics Committee. Due to its retrospective nature, informed consent for the use of the clinical records of each patient was waived.

Included participants were adults (≥ 18 years old) diagnosed with T1D for more than 1 year and under SGLT2i therapy started until 30th June 2021 and for more than 3 months at the time of data analysis. Per protocol, individuals had to present blood ketone levels <0.6 mmol/L on a regular evaluation, performed before and during treatment with SGLT2i, and use an intermittent or real time CGM systems with a percentage of active time from the last 14 days >70%. Prior to the introduction of SGLT2i, all participants were properly instructed on the precautions to be taken during its administration and how to proceed in case of symptoms and/or signs suggestive of DKA. A document summarizing all this information was always provided.

Exclusion criteria. The individuals who, in the beginning or during the study period, changed to ultra-rapid-acting insulins, upgraded to integrated insulin delivery systems or started another adjuvant therapy (namely metformin or GLP1 agonists) were excluded from the study. Pregnant patients and women in pre-conception evaluation were also excluded, as were patients that already took SGLT2i before starting CSII treatment had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 using the 2009 CKD-EPI creatinine equation, ingested a low-carb diet and whenever significant data were missing (Levey et al. 2009).

Data collection. Demographic and clinical data were retrieved from medical records, including age at the time of data analysis, gender, years of T1D diagnosis, known chronic complications of diabetes, previous history of acute complications, namely severe hypoglycemia and DKA, type of insulin in use, type and moment of SGLT2i introduction and other antihyperglycemic agents used. Ambulatory glucose profile (AGP) report of the last 28 days was evaluated at the moment of SGLT2i introduction (T0), and after 3 months (T3M), 6 months, (T6M) and 12 months (T12M) of use. In these 4 different moments, the following data were collected: mean glucose, glucose management indicator (GMI), time in range (TIR; glucose between 70 to 180 mg/dL), time above range (TAR; glucose >180 mg/dL) and time below range (TBR; glucose <70 mg/dL), weight, HbA1c, total daily dose of insulin (TDDI) and proportion of daily basal insulin dose to TDDI. SGLT2i-related complications, namely the occurrence of DKA or genital infections, were also assessed. All drug withdrawals were registered, as was its timing and motive.

Statistical analysis was performed using the IBM Statistical Package for Social Sciences for Windows version 27.0 (IBM Corporation, USA). The normality

of data distribution of numeric variables was evaluated through the Kolmogorov-Smirnov test. Non-normal continuous variables were described as median value and interquartile range (IQR) and normal continuous variables as mean value and standard deviation (SD). McNemar's test was applied for categorical related variables, and paired-sample T-Test and Wilcoxon signed-rank test were used for normal and non-normal continuous related variables, respectively. Two-sided p-value<0.05 was considered statistically significant.

Results

Of 172 T1D individuals under CSII therapy, 34 were treated with SGLT2i. Of these, 23 were included in the study. Figure 1 specifies the exclusion criteria of the remaining 11 individuals. Demographic and clinical characteristics of participants are shown in Table 1: 14 (60.9%) were female with a mean age of 45.9±11.6 years and a mean diabetes duration of 27.7±11.7 years. Mean time under CSII was 9.4±4.6 years and mean follow-up time since the beginning of SGLT2i was 25.5±6.9 months. In 21 (91.4%) individuals, dapagliflozin (5 mg/day) was the drug used. Six patients (26.1%) were also treated with metformin.

Comparing with the moment of SGLT2i introduction (T0), after 3, 6, and 12 months, there was a statistically significant increase of TIR (Δ_{T3M}=12.8%, p<0.001; Δ_{T6M}=11.5%, p <0.001; Δ_{T12M}=11.1%, p<0.001) and a decrease in TAR (Δ_{T3M}=13.6%, p<0.001; Δ_{T6M}=11.9%, p<0.001; Δ_{T12M}=10.5%, p<0.001). There were no statistical differences in TBR (Figure 2). The proportion of individuals with TIR ≥70% increased from 26.1% (n=6) to 66.7% (n=14) (p=0.008), 59.1% (n=13) (p=0.038), and 52.4% (n=11) p=0.125, at T3M, T6M and T12M, respectively (Figure 3).

The mean glucose and the GMI significantly decreased in the 3 evaluated moments. HbA1c reduced as well during the 12-month period (Table 2).

After 6 and 12 months of treatment, a significant reduction in median weight (Δ_{T6M} = 2 kg, p=0.007; Δ_{T12M} = 4.5 kg, p=0.003) and median body mass index (BMI) (Δ_{T6M} = 1.5 kg/m^2, p=0.005; Δ_{T12M} = 1.1 kg/m^2, p=0.002) was observed (Table 2).

Ten participants presented data of both TDDI at T0M and T12M. After 12 months, the median TDDI significantly decreased by 8.4% (Δ_{T12M} = 3 UI, p=0.021) but the proportion of daily basal insulin dose to TDDI did not change (Table 2).

Two patients (8.7%; CI 95%: 0.02–0.25) developed mild euglycemic DKA during SGLT2i treatment, both under dapagliflozin 5 mg and with diagnosis made due to active determination of ketone levels at home. One case occurred after 6 months of therapy in one woman in their 50s, with a dental infection. The episode was completely resolved after appropriate evaluation and treatment in the emergency room in less than 24 h with no need for hospitalization. As additional risk factors to DKA, she presented a BMI of 24.5 kg/m^2 and three months TDDI reduction of 26.9% (8.4 UI). The other episode developed after 5

Table 1
Demographics and clinical characteristics of participants

Parameter	Value
Total number (n)	23
Females (n, %)	14 (60.9%)
Age (years)[a]	45.9±11.6
Diabetes duration (years)[a]	27.7±11.7
Time under CSII treatment (years)[a]	9.4±4.6
Glucose monitoring system in use	
Intermittently Scanned CGM (n, %)	23 (100%)
Chronic complications (n, %)	13 (56.5%)
Chronic microvascular complications	12 (52.2%)
Retinopathy (n, %)	10 (43.5%)
Neuropathy (n, %)	1 (4.3%)
Nephropathy (n, %)	4 (17.4%)
Chronic macrovascular complications	2 (8.7%)
Coronary heart disease (n, %)	2 (8.7%)
Cerebrovascular disease (n, %)	–
Peripheral artery disease (n, %)	–
History of acute complications	3 (13.0%)
Severe hypoglycemia (n, %)	3 (13.0%)
Diabetic ketoacidosis (n, %)	–
SGLT2i used as adjuvant treatment to insulin	
Dapaglifozin 5 mg/day (n, %)	21 (91.4%)
Empagliflozin 5 mg/day (n, %)	1 (4.3%)
Ertugliflozin 15 mg/day (n, %)	1 (4.3%)
Mean follow-up since the beginning of SGLT2i (months)[a]	25.5±6.9
Other adjuvant treatment started before SGLT2i	
Metformin (n, %)	6 (26.1%)
Cr (mg/dL)[a]	0.8±0.1
GFR (mL/min/1.73m^2)[b]	101.1 (24.2)

[a]Data are presented as mean±standard deviation. [b]Data are presented as median (interquartile range). Abbreviations: CGM – continuous glucose monitoring; Cr – creatinine; CSII – continuous subcutaneous insulin infusion; GFR – glomerular filtration rate; SGLT2i – sodium-glucose cotransporter 2 inhibitor.

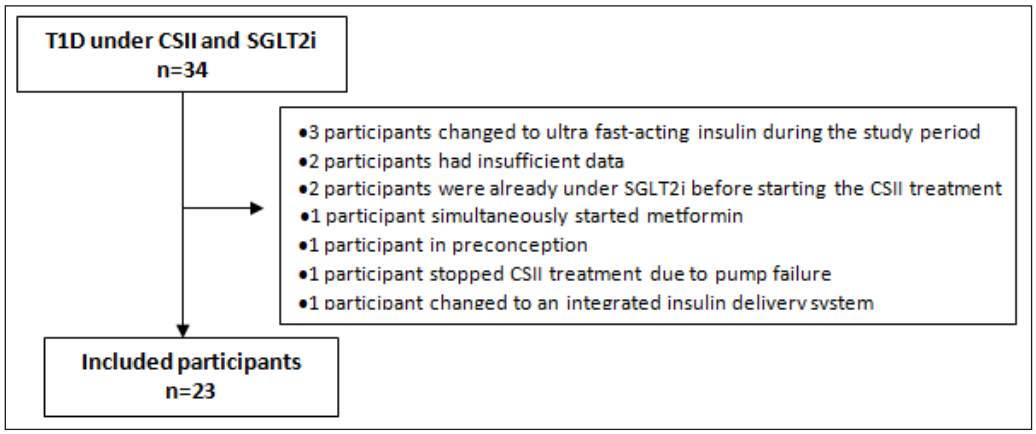


Figure 1. Flowchart of participants included. Abbreviations: CSII – Continuous Subcutaneous Insulin Infusion; SGLT2i – sodium glucose cotransporter 2 inhibitor; T1D – type 1 diabetes.

months of SGLT2i treatment in one woman in their 40s, probably due to an infusion set occlusion. She was on a very low carb diet (ingestion <75 g of carbs per day), had a BMI of 26.1 kg/m^2 and her TDDI reduced by 5% (2 UI) in 3 months of therapy. This participant was hospitalized during two days.

Besides these 2 individuals that stopped treatment due to DKA, only one more had to suspend SGLT2i, after a diagnosis of prostatitis.

No severe hypoglycemia was registered since SGLT2i introduction and no other risk factor for DKA development was identified.

Discussion

In the present study, we showed the efficacy of adjuvant treatment with SGLT2i in subjects with T1D under CSII. There was a significant reduction in mean glucose value and GMI and a significant increase in TIR, which remained stable during 12 months of analysis. These positive results were not accompanied by an increase in TBR or occurrence of severe hypoglycemia. This increment of TIR was greater than 5%, which according to the recommendations from the international consensus on TIR is considered clinically relevant (Battelino et al. 2019).

Several clinical trials performed with empagliflozin, dapagliflozin, canagliflozin, and sotagliflozin have been carried out to assess the efficacy and safety of these drugs in T1D (both under multiple administrations of insulin and insulin pump) and all concluded the same: SGLT2i significantly improve TIR on AGP, without increasing TBR, and reduce HbA1c, blood pressure and TDDI (Henry et al. 2015; Dandona et al. 2017, 2018; Garg et al. 2017; McCrimmon and Henry 2018; Rosenstock et

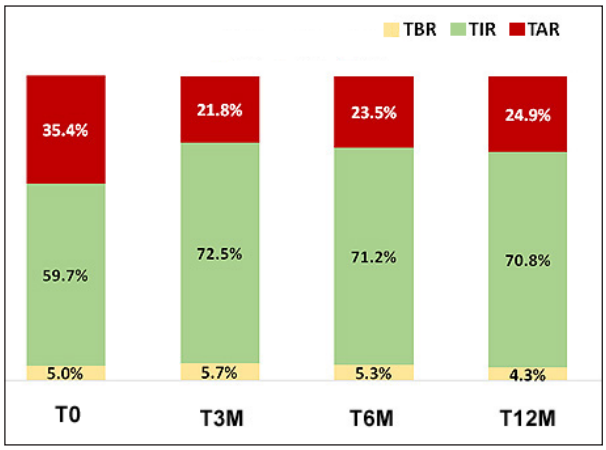


Figure 2. Comparison of times in range, time above range, and time below range before SGLT2i introduction and after 3, 6, and 12 months of treatment. Abbreviations: TAB – time above range; TBR – time below range; TIR – time in range.

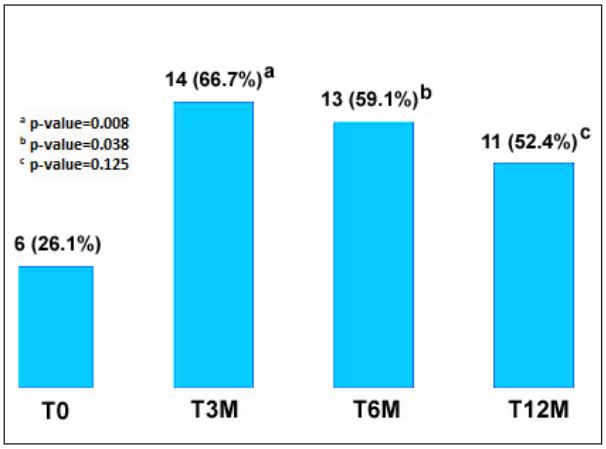


Figure 3. Number of individuals with time in range ≥70% before the introduction of SGLT2i (T0) and after 3, 6, and 12 months of treatment.

Table 2
Comparison of glycemic control, insulin need and weight before SGLT2i introduction and after 3, 6 and 12 months of treatment

Parameter	T0	n	T3M	n	p-value	T6M	n	p-value	T12M	n	p-value
HbA1c (%)[a]	7.4±0.8	21	7.1±0.6	10	0.022	6.9±0.8	14	0.098	6.9±0.6	13	0.530
GMI (%)[a]	7.2± 0.8	21	6.6±0.7	18	0.001	6.7±0.8	22	<0.001	6.8±0.5	20	0.006
Mean glucose (mg/dL)[a]	163.0±21.4	23	143.2±21.2	20	0.001	147.9±24.5	21	0.001	151.8±16.7	16	0.001
TAB (%)[a]	35.4±15.0	23	21.8±13.5	21	<0.001	23.5±15.0	22	<0.001	24.9±10.1	21	<0.001
TIR (%)[a]	59.7±14.7	23	72.5±12.7	21	<0.001	71.2±14.5	22	<0.001	70.8±10.8	21	<0.001
TBR (%)[a]	5.0±2.9	23	5.7±3.9	21	0.450	5.3±4.1	22	0.736	4.3±2.6	21	0.143
Total daily insulin dose (UI)[b]	35.6 (23.1)	17	41.0 (15.3)	16	0.050	37.5 (27.4)	14	0.059	34.7 (20.6)	15	0.021
Basal insulin (%)[b]	44.0 (9.5)	17	42.0 (5.0)	16	0.789	40.0 (13.3)	14	0.824	44.0 (10.0)	15	0.095
Weight (kg)[b]	71.0 (14.0)	23	66.5 (18.8)	16	0.227	69.0 (17.0)	19	0.007	66.5 (13.0)	18	0.003
BMI (kg/m^2)[b]	26.0 (3.0)	23	24.9 (2.9)	16	0.198	24.5 (3.4)	19	0.005	24.9 (2.6)	18	0.002

[a]Data presented as mean±standard deviation. [b]Data presented as median (interquartile range). Abbreviations: BMI – body mass index; GMI – glucose management indicator; SGLT2i – sodium-glucose cotransporter 2 inhibitor; TAR – time above range; TBR – time below range; TIR – time in range; UI – Units of insulin.

al. 2018). We report an improvement of TIR in 12.8%, 11.5%, and 11.1% at 3, 6, and 12 months after starting SGLT2i, similar to those achieved in these studies. Empagliflozin as adjunctive to insulin therapy trial (EASE) showed an increase of TIR in 12% after 52 weeks with empagliflozin 10 mg therapy and the dapagliflozin evaluation in patients with inadequately controlled T1D (DEPICT) clinical trial program verified that after 24 weeks of treatment with 5 mg of dapagliflozin, the TIR increased by 9.1% (Dandona et al. 2017; Rosenstock et al. 2018).

More recently, studies have been published specifically on people with T1D under CSII showing similar results. In a 2×2 factorial randomized placebo-controlled trial assessing 4 weeks of closed-loop delivery vs. sensor-augmented pump treatment and empagliflozin vs. placebo. Haidar et al. (2022) have shown that groups under SGLT2i had higher TIR compared to placebo groups. Another randomized, controlled crossover study in adults with T1D under CSII also concluded that participants receiving empagliflozin had higher daytime TIR vs. placebo participants (Garcia-Tirado et al. 2022).

We also verified that SGLT2i has a significant impact on weight with a mean loss of 4.5 kg in 12 months. This result was already recognized in previous publications as in EASE trial, which showed a loss of 3.0 kg in 52 weeks with empagliflozin 10 mg and in DEPICT with a documented loss of 3.5 kg and 2.3 kg with dapagliflozin 5 mg and 10 mg, respectively, in 6 months (Dandona et al. 2017; Rosenstock et al. 2018). This weight loss can be justified mainly by the mechanism of action of SGLT2i as this pharmacological class impairs renal glucose reabsorption, promotes osmotic diuresis, and glucosuria in an insulin-independent manner leading to calorie loss and volume depletion (McCrimmon and Henry 2018; Rosenstock et al. 2018). Other underlying mechanisms that have been postulated are the reduction in daily dose of insulin requirements and a shift to free fatty acid and amino acids substrate utilization due to the decrease plasma glucose and insulin levels with increments in glucagon release, leading to stimulation of lipolysis, lipid oxidation, and proteolysis (DeFronzo et al. 2017; Lee et al. 2018).

Regarding of changes in TDDI, we verified a median reduction of 8.4% at 12 months. This value is similar to those described in other studies and within the recommended reduction to prevent the development of DKA (Rosenstock et al. 2018; Danne et al. 2019).

Euglycemic DKA is an uncommon condition ranging between 2.6% to 3.2% of all the DKA cases (Nasa et al. 2021). However, the use of SGLT2i in T1D significantly increases the risk for euglycemic DKA, which has been a main concern that has limited its prescription (Henry et al. 2015; Dandona et al. 2017, 2018; Mathieu et al. 2016, 2018; Rosenstock et al. 2018). The EASE described from two to threefold increase in DKA risk in the empagliflozin group being that risk dose related (Rosenstock et al. 2018). The DEPICT clinical trial program also found a higher incidence of DKA in the dapagliflozin groups compared with placebo (dapagliflozin 10 mg: 2.2–3.4% vs. dapagliflozin 5 mg: 2.6–4.0% vs. placebo 0–1.9%) (Dandona et al. 2017, 2018; Mathieu et al. 2018). In

both these studies, about a third of participants was treated with CSII. Due to this association (in October 2021), AstraZeneca, in agreement with the European Medicine Agency (2021), has taken the decision to remove the T1D indication for dapagliflozin.

In our study, during the 12-month period, 2 participants developed mild euglycemic DKA (8.7%) a higher prevalence comparing with the results previously published. Both cases occurred in the patients with risk factors for DKA. They both were women with a BMI <27 kg/m^2 and the diagnosis was made due to active determination of ketone levels at home. Lower BMI is a known risk factor for the development of DKA (Danne et al. 2019). A multicenter, randomized, double-blind, phase 3 trial with ipragliflozin for 24 weeks, showed that a higher BMI is associated with a lower risk of DKA (Kaku et al. 2019). Haidar et al. (2022) have also verified that the mean ketone levels in participants with empagliflozin was significantly lower for BMI ≥27 kg/m^2. These findings are probably related to the higher insulin requirements in people with higher body weight to the rate of lipolysis and consequently the production of ketone bodies, which is lower the higher the BMI (Cifuentes et al. 2008).

Other well documented risk factors for ketosis and DKA are the occurrence of episodes of acute illness of any sort, infusion set problems, and a TDDI reduction greater than 10–20% (Danne et al. 2019). Accordingly, in this study, one case of DKA occurred due to an acute dental infection and the other after an infusion set occlusion. In one of them, a TDDI reduction of 26.9% after 3 months of treatment was verified.

Despite this DKA risk, due to its proven metabolic benefit and potential cardiorenal protection, we still believe that benefits outweigh the risks, provided that adequate selection of patients is made. The incidence of DKA was not negligible; however, both cases were mild, timely recognized, and easily managed.

The major limitations of this study are its retrospective nature and its small sample size that can mitigate the true incidence of SGLT2i-associated complications. Additionally, we point out the fact that the evaluation occurred during the pandemic where the routines and lifestyle of participants were changed. Many recent publications have shown an improvement of glycemic control in T1D individual during the lockdown in pandemic period (Avari et al. 2021). Therefore, the development of our study during this period may have contributed for the outcomes reported.

One of the main strengths of this work is the fact that it is a real-life study with the advantage of better representing the population that we effectively evaluated in our clinical practice. This feature may in part explain the higher percentage of euglycemic DKA found. In addition, our study supports the good results of these drugs in the subgroup of individuals under CSII, about which publications are still scarce.

To conclude, the use of SGLT2i as an adjuvant treatment in individuals with T1D under pump insulin was associated with a significant increase of TIR without increasing the risk and the time in hypoglycemia. However, the risk of DKA is real. Careful selection of participants, proper education, and development of risk-mitigation strategies as cautious reductions in insulin doses during the follow-up and frequent fingerstick ketone monitoring by participants, are fundamental to reduce the occurrence of DKA (Danne et al. 2019). In the future, the development of more real-life studies in T1D populations under CSII will be extremely important to confirm these results and the benefits of using this pharmacological class.

Conflict of interest: *The authors declare no conflict of interest.*

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