*Rev Port Endocrinol Diabetes Metab. 2022;***17(3-4)**

Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Use of SGLT2 Inhibitors in Type 1 Diabetes: Experience from a Portuguese Tertiary Center

Mariana Aveiro-Lavrador [a,*], Bárbara Araújo [a], Miguel Melo [a,b], Luísa Barros [a], Isabel Paiva [a]

[a] *Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[b] *Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal.*

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2022-06-21
Accepted/Aceite: 2022-11-01
Publicado / Published: 2023-01-18

Keywords:
Diabetes Mellitus, Type 1/drug therapy;
Sodium-Glucose Transporter 2 Inhibitors/therapeutic use.

A B S T R A C T

Introduction: Basal-bolus insulin management remains the only option for effective treatment of type 1 diabetes (T1DM). However, most of T1DM patients do not achieve glycemic targets and so there has been a great interest in adjunct therapies, as the use of SGLT2 inhibitors (SGLT2i). Our study aimed to assess the impact of introducing an SGLT2i on glycemic control, weight, and insulin doses in a group of T1DM patients.
Methods: A retrospective longitudinal study was conducted in the Endocrinology Department of a University Hospital. Inclusion criteria comprised T1DM patients, under intensive basal-bolus insulin therapy (continuous subcutaneous insulin infusion-CSII, or multiple daily injection), who initiated therapy with an SGLT2i and with regular use of freestyle libre®. CGM metrics, daily insulin dose, glucose levels, body weight, and body mass index were evaluated, using the ambulatory glucose profile (AGP), Libreview®, and patients' clinical records, before and after 3 months of dapagliflozin introduction. Statistical analysis was performed using IBM SPSS Statistics v.26 for Windows.
Results: 17 patients were included with a mean age of 36.12 years (SD=11.061), 58.82% female, 64.71% under CSII and 35.293% under multiple daily injection. After the introduction of dapagliflozin, there was an overall improvement in glycemic control, with statistically significant differences in the following parameters: %time in range (50.9% to 60.2%; p=0.019); coefficient of variation (43.7±6.2% to 40.7 ±6.4%; p=0.001); GMI (7.6% to 7.0%; p=0.001); total insulin daily dose (53.9 U to 44.0 U; p=0.001); basal insulin dose (30.0U to 25.0U; p=0.001); prandial insulin dose (24.7 to 20.0U; p=0.028). At the same time, median fasting glucose, pre and post-lunch and pre-dinner glucose were significantly reduced, as well as body weight and BMI. Regarding the difference of glucose levels with and without dapagliflozin in the various periods of the day, the median was higher at post-lunch period (-35.45 mg/dL IQR: -44.0, -10.22) and lower at post-dinner time (-6.31 mg/dL, IQR: -46.78, 2.105).
Conclusion: The introduction of SGLT2i in this population improved glycemic control during pre and postprandial periods. The maximal effect was observed in post-lunch period, possibly because of the therapeutic prescription schedule.

Palavras-chave:
Diabetes Mellitus Tipo 1/tratamento farmacológico;
Inibidores do Transportador 2 de Sódio-Glicose/uso terapêutico.

Uso de Inibidores SGLT2 na Diabetes Tipo 1: Experiência de um Centro Terciário Português

R E S U M O

Introdução: A utilização de insulina em regime basal/bolus constitui atualmente a única terapêutica efetiva para a diabetes *mellitus* (DM) tipo 1. Contudo, a maioria dos doentes não atinge os alvos glicémicos, havendo um crescente interesse na utilização de fármacos coadjuvantes. A utilização dos inibidores SGLT2 (SGLT2i) tem merecido especial atenção. O nosso estudo teve como objetivo avaliar o impacto da sua introdução no controlo glicémico, no peso e nas doses de insulina num grupo de doentes com DM tipo 1.

* Autor Correspondente / Corresponding Author.
E-Mail: mariana.lavrador@hotmail.com (Mariana Aveiro Lavrador)
Praceta Professor Mota Pinto, 3004-561 Coimbra, Portugal

https://doi.org/10.26497/ao220037

Métodos: Estudo longitudinal retrospetivo que incluiu diabéticos tipo 1, sob insulinoterapia intensiva (perfusão subcutânea contínua de insulina – PSCI ou múltiplas administrações diárias), e com uso regular de freestyle libre®, em quem foi iniciada terapêutica com SGLT2i. Foram considerados os dados relativos às métricas da monitorização contínua de glicose, dose diária de insulina, níveis de glicose, peso corporal e IMC. Avaliados os dados constantes no processo clínico e no ambulatory glucose profile (AGP) e Libreview®, antes e após 3 meses da introdução da dapagliflozina. A análise estatística foi desenvolvida através do SPSS Statistics v.26.
Resultados: Foram incluídos 17 doentes com uma média de idades de 36,12 anos (DP=11,061), 58,82% do sexo feminino, 64,71% sob PSCI e 35,293% sob múltiplas administrações. Após introdução da dapagliflozina, verificou-se uma melhoria global do controlo glicémico, com diferenças estatisticamente significativas nos seguintes parâmetros: %tempo no alvo (50,9% *vs* 60,2%; *p*=0,019); coeficiente de variação (43,7±6,2% *vs* 40,7 ±6,4%; *p*=0,001); GMI (7,6% *vs* 7.0%; *p*=0,001); dose diária total (53,9 U *vs* 44,0 U; *p*=0,001); dose de insulina basal (30,0U *vs* 25,0U; *p*=0,001) e dose de insulina prandial (24,7U *vs* 20,0U; *p*=0,028). As medianas da glicemia do jejum, glicemia pré e pós-almoço e pré-jantar reduziram significativamente, assim como o peso e o IMC. Em relação às diferenças nos níveis de glicose antes e depois da dapagliflozina nos vários períodos do dia, a mediana foi maior no período pós-almoço (-35,45 mg/dL AIQ: -44,0; -10,22) e menor no período pós-jantar (-6,31 mg/dL, AIQ: -46,78; 2,105).
Conclusão: A introdução da dapagliflozina melhorou o controlo glicémico, cobrindo os períodos pré e pós-prandiais. O efeito máximo foi observado no período após o almoço, o que poderá associar-se à posologia utilizada.

Introduction

Glycemic control in people with type 1 diabetes (T1DM) reduces the risk of microvascular and macrovascular complications.[1] The mainstay of treatment requires the administration of both basal and prandial insulin, trying to mimic the physiologic secretion of insulin. Basal-bolus insulin management remains the only option for effective treatment of type 1 diabetes.

Despite the recent exponential improvement in therapeutic approaches, namely the use of insulin pumps, continuous glucose monitoring (CGM) and hybrid closed-loop systems, the risk of hypoglycemia and weight gain associated with insulin still exist, and the latter are barriers to optimal use of insulin therapy. As a consequence, most of T1DM patients do not achieve glycemic targets.[2]

In this context, there has been a great interest in adjunct therapies for T1DM to help improving glycemic control.[2] The majority of noninsulin therapies approved for type 2 diabetes are not effective in T1DM. Recently, a new approach was performed, using sodium–glucose cotransporter (SGLT) inhibitors as an adjunct to insulin therapy in T1DM.[3] This pharmacological class blocks SGLT type 1 transporter in the intestinal tract, delaying dietary glucose absorption (SGLT1 inhibitors),[4] and blocks SGLT type 2 transporter in the proximal tubule of the kidney resulting in glycosuria and natriuresis (SGLT2 inhibitors). SGLT inhibitors act independently of insulin to facilitate the improvement of glycemic control without exacerbating insulin adverse effects, such as hypoglycemia and weight gain.[3]

Initially used off-label, dapagliflozin, an SGLT2 inhibitor, received the approval by EMA for its use as adjunctive therapy in T1DM patients, in 2019.[5] Oral dapagliflozin was then approved in the EU at a dosage of 5 mg/day as an adjunct to insulin in adults with type 1 diabetes (T1DM) and a body mass index (BMI) of≥27 kg/m^2, when insulin alone does not provide adequate glycemic control despite optimal insulin therapy. In the phase III DEPICT-1[6] and -2[7] trials, use of dapagliflozin 5 mg/day as an adjunct to insulin improved glycemic control and reduced total daily insulin dose and body weight relative to placebo in adults with inadequately controlled T1DM, over 24 weeks of treatment. Dapagliflozin was generally well tolerated with a good safety profile and a hypoglycemia profile generally similar to placebo.[8] However, higher frequency of diabetic ketoacidosis (DKA) was consistently reported in patients with type 1 diabetes, and specific risk minimization measures to health care providers and patients were recommended by EMA. Similar results were obtained in inTandem clinical trial that assessed efficacy and safety of sotagliflozin combined with insulin therapy for the treatment of patients with T1DM.[9,10] and in the EASE clinical trial that tested empagliflozin.[11] Recently, the indication for dapagliflozin use in type 1 diabetes was withdrawn by the pharmaceutical company.[12]

Apart from DKA, the use of this drug class has other potential associated adverse effects, so it is mandatory to increase the knowledge and to recognize the best criteria that allow the optimal use in T1DM.

The present work aimed to assess the impact of introducing an SGLT2i on glycemic control, weight and insulin doses in a group of patients with T1DM.

Material and Methods

A retrospective longitudinal study was conducted in people with type 1 diabetes followed in the Endocrinology Department of a University Hospital. Inclusion criteria comprised T1DM patients under intensive basal-bolus insulin therapy (continuous subcutaneous insulin infusion-CSII, or multiple daily injection - MDI) who initiated therapy with an SGLT2i (dapagliflozin 10 mg once a day, dapagliflozin 10mg ½ pill once a day, or the association dapagliflozin/metformin 5/850 mg once a day). Regular use of freestyle libre®, considered as at least 70% of time CGM is active in the last 14 days, was also an inclusion criteria. The exclusion criteria comprised people under 18 years, pregnant women, body mass index (BMI) <27 kg/m^2, evidence of insulin omissions (in non-adherent patients), insulin exchanges, and patients who were prescribed with new drugs with potential effects on glycemia and weight during study period. Patients with history of pancreatic disorders resulting in decreased β-cell function, signs of poorly controlled diabetes (including DKA requiring medical intervention or hospitalization for hyperglycemia or hypoglycemia in the previous month), and unstable renal disease were also excluded.

Patients' clinical records were appraised to evaluate sociodemographic data and the following clinical information at baseline: duration of type 1 diabetes; method of insulin delivery; mean total insulin dose; mean body weight/BMI; estimated glomerular filtration rate (eGFR). The presence of diabetic nephropathy (defined as the presence of urinary albumin ≥300 mg/g creatinine and/or

an estimated glomerular filtration rate <60 mL/min/1.73 m^2), diabetic retinopathy (defined as the diagnosis of nonproliferative or proliferative retinopathy by an experienced ophthalmologist) and diabetic neuropathy (presence of distal symmetric polyneuropathy or autonomic neuropathy) were also assessed, as well as the existence of previous macrovascular complications (stroke, myocardial infarction and peripheral artery disease).

The following data were assessed, before and after 3 months of treatment, using the ambulatory glucose profile (AGP) from the previous 14 days and other glucose data from libreview® platform: glucose management indicator (GMI); coefficient of variation (CV); percentage and mean value of time in range, defined as glucose levels between 70 and 180 mg/dL (%TIR); percentage and mean value of time above range, defined as glucose levels > 180 mg/dL (%TAR); percentage and mean value of time below range, defined as glucose levels <70 mg/dL (%TBR). Levels of fasting glucose, pre-meal glucose (lunch and dinner), 2 hours post-meal glucose (lunch and dinner), and postprandial glucose excursion (lunch and dinner) were assessed using the glucose values available in the section "transfer glucose data" of the Libreview platform. Total daily insulin dose (TDD), basal dose, prandial dose, body weight and BMI were also evaluated.

The occurrence of genital infections, severe hypoglycemia (level 3 hypoglycemia) and DKA were also registered.

Statistical analysis was performed using IBM SPSS Statistics v.26 for Windows.

To characterize the study population, means with standard deviations (SD) or medians with interquartile ranges (IQR) were calculated for continuous data. For categorical variables, the absolute numbers and percentage proportions were used. The Shapiro–Wilk (SW) and Kolmogorov-Smirnova tests were used to assess the normality of data.

Differences between groups were evaluated using the non-parametric paired test Wilcoxon signed-rank or paired sample t-test. *p* values lower than 0.05 were considered as significant.

Results

The study included 17 patients with a mean age of 36.12 years (SD =11.06) ranging from 22 to 61 years. A percentage of 58.82% of the population were female. Baseline characteristics of included patients are discriminated in Table 1.

The patients included had a mean duration of T1DM of 17.65 (±9.50) years and the majority (64.7%) was under CSII. Regarding body weight and BMI, the mean was 88.71 kg and 30.79 kg/m^2, respectively.

In what concerns to eGFR, the mean was 96.96 mL/min/1.73 m^2, compatible with normal kidney function.

After the introduction of dapagliflozin, there was an overall improvement in glycemic control.

Statistical difference was found in TIR after 3 months of the introduction of the drug, increasing from 50.9% to 60.2% (*p*=0.019), reflecting an additional 2.78 hours of time spent in range every day (*p*=0.006). Both the CV and GMI decreased significantly from 43.7±6.2% to 40.7 ±6.4% (*p*=0.001) and 7.6% (7.2-9.2) to 7% (6.7-7.5) (*p*=0.001), respectively (Table 2).

The median of fasting glucose 3 months after the introduction of dapagliflozin decreased from 161.9 to 144.9 (*p*=0.023), as well as the levels of pre-meal glucose at lunch and dinner and post-meal glucose at lunch, that reduced significantly (Table 3). A reduction in %TAR was also found, although with no statistical significance (41.5% to 32.2%, *p*=0.058). Similarly, there was a mean reduction of 2.15 hours of time spent above range (*p*=0.063). In what concerns to TBR, there was no statistical difference after the use of this SGLT2i.

In relation to the difference of glucose levels with and without dapagliflozin in the various periods of the day, the median was higher for post-lunch period (-35.47 mg/dL IQR: -44.0, -10.22) and lower for post-dinner time (-6.31 mg/dL, IQR: -46.78, 2.05) – Table 4.

Regarding postprandial glucose excursion, there was no statistical difference in this parameter with the use of dapagliflozin. However, at lunch time, there was an improvement in glucose ex-

Table 1. Baseline characteristics of included patients

Age (years), mean (± SD)	36.12 (± 11.06)
[20-29]	7 (41.18%)
[30-39]	4 (23.53%)
[40-49]	4 (23.53%)
[50-59]	1 (5.88%)
[60-69]	1 (5.88%)
Range	22-61
Females, *n* (%)	10 (58.82%)
Duration of type 1 diabetes (years), mean (± SD)	17.65 (±9.50)
Range	3-32
Treatment	
Dapagliflozin 5 mg	7 (41.18%)
Dapagliflozin 10 mg	2 (11.76%)
Dapagliflozin/metformin 5/850 mg	8 (47.06%)
Method of insulin delivery	
CSII, n (%)	11 (64.71%)
MDI, n (%)	6 (35.29%)
Total daily insulin dose (IU/kg/day), mean (± SD)	0.71 (± 0.37)
Body weight (kg), mean (± SD)	88.71 (± 14.82)
BMI (kg/m^2), mean (± SD)	30.79 (±3.11)
eGFR (mL/min/1.73 m^2), mean (± SD)	96.96 (±19.87)
Microvascular complications, n (%)	4 (23.53%)
Diabetic retinopathy	4
Macrovascular complications, n (%)	2 (11.76%)
Stroke	1
Myocardial infarction	1

TSD: standard deviation; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injection.

Table 2. CGM metrics, body weight and BMI before and after introduction of dapagliflozin.

	Before SGLT2i	After SGLT2i	*p*-value*
TIR (%), mean (± SD)	50.9 (± 13.4)	60.2 (±14.7)	0.019
TIR (minutes), mean (± SD)	710.7 (±178.5)	877.2 (±203.6)	0.006
TAR (%), mean (± SD)	41.5 (±15.2)	32.2 (±15.9)	0.058
TAR (minutes), mean (± SD)	588.8 (±212.6)	460.0 (±227.0)	0.063
TBR (%), median (IQR)	6.0 (2,5-12)	7.0 (4-11)	0.521
TBR (minutes), mean (± SD)	116.9 (±105.9)	103.7 (±55.3)	0.567
CV (%), mean (± SD)	43.7 (±6.2)	40.7 (±6.4)	0.001
GMI (%), median (IQR)	7.6 (7.2-9.2)	7.0 (6.7-7.5)	0.001
Weight (kg), mean (± SD)	88.7 (±14.8)	84.3 (±13.6)	<0.001
BMI (kg/m^2), mean (± SD)	30.8 (±3.1)	29.3 (±2.9)	<0.001

* t-test or Wilcoxon

SD: standard deviation; IQR: interquartil range; TIR: time in range; TAR: time above range; TBR: time below range; CV: coefficient of variation; GMI: glucose management indicator; BMI: body mass index

Table 3. Daily insulin dose and glucose levels before and after introduction of dapagliflozin.

	Before SGLT2i	After SGLT2i	*p*-value*
Fasting glucose (mg/dL), mean (± SD)	169.9 (±30.4)	147.8 (±25.6)	0.028
Pre-meal glucose – lunch (mg/dL), mean (± SD)	178.3 (±36.1)	162.3 (±25.7)	0.028
Pre-meal glucose – dinner (mg/dL), mean (± SD)	173.4 (±55.8)	145.1 (±25.2)	0.025
Post-meal glucose – lunch (mg/dL), mean (± SD)	185.5 (±37.9)	158.4 (±27.8)	0.006
Post-meal glucose – dinner (mg/dL), median (IQR)	195.6 (±34.9)	171.5 (±34.9)	0.078
Postprandial glucose excursion – lunch (mg/dL), mean (± SD)	7.2 (±49.3)	-4.5 (±33.3)	0.290
Postprandial glucose excursion – dinner (mg/dL), mean (± SD)	22.2 (±45.0)	28.9 (±45.9)	0.492
TDD (U), median (IQR)	53.9 (46.5-72.5)	44.0 (40.0-64.9)	0.001
Basal dose (U), median (IQR)	30.0 (26.4-40.0)	25.0 (23.7-33.1)	0.001
Bolus dose (U), median (IQR)	24.7 (19-39.8)	20.0 (15.0-28.3)	0.028

* t-test or Wilcoxon

SD: standard deviation; IQR: interquartil range; TDD: total daily dose

Table 4. Difference between glucose levels after and before dapagliflozin.

Fasting period (median, IQR)	Pre-lunch period (median, IQR)	Post-lunch period (median, IQR)	Pre-dinner period (median, IQR)	Post-dinner period (median, IQR)
-28.77 (-51.48, -12.46)	-20.15 (-35.03, -1.01)	-35.47 (-44.0, -10.22)	-19.12 (-65.11, -1.81)	-6.31 (-46.78, 2.05)

cursion with SGLT2i, with a mean of -4.5 mg/dL (±33.3) versus 7.2 (±49.3) without the drug. Conversely, in what concerns to glucose excursion at dinner time, glucose levels were higher after the introduction of SGLT2i (22.2 ±45.0 mg/dL *vs* 28.9 ±45.9 mg/dL).

Median total daily insulin dose (TDD) reduced significantly from 53.9 U to 44.0 U (p=0.001), as well as basal insulin dose and bolus, which decreased from 30.0 U to 25.0 U (p=0.001) and from 24.7 to 20.0 U (p=0.028), respectively (Table 3).

There was also a statistically significant reduction in weight, with an average value of 4.4 kg (p<0.001) and in BMI, with an average value of 1.51 kg/m^2 (p<0.001) (Table 2).

More than half of the patients (9/17; 52.9%) were taking dapagliflozin alone (7 at the 5 mg dose and 2 at the 10 mg dose) and 8 patients were taking the association with metformin. The independent analysis for patients on monotherapy with dapagliflozin showed a similar trend to that found for the total series, with significant differences in %CV (p=0.012), GMI (p=0.015), post-meal glucose lunch (p=0.019), postprandial glucose excursion – lunch (p=0.008) and weight (p=0.002). Also, the %TIR improved with the introduction of dapagliflozin, although with no statistical difference (58.33% ±14.13 with dapagliflozin *vs* 50.67 % ±16,01, p=0.108). There were no episodes of severe hypoglycemia or ketoacidosis during the study period. Additionally, only 1 patient had a genital infection that did not require treatment interruption.

Discussion

Our study suggests that the introduction of dapagliflozin in T1DM patients led to an overall improvement in glycemic control, with a more pronounced effect on lunch post-prandial glucose levels. Based on the CGM data, time in the target glycemic range, %CV and GMI showed significant improvements. In fact, more than 60% of the CGM readings were in the target range 3 months after the introduction of dapagliflozin, reflecting an additional 2.78 hours of time spent in range every day. These findings are in line with those obtained in DEPICT-2 trial,[7] where 50% of the CGM readings were in target range at week 24. However, no statistical significance was found for %TAR and %TBR, results that are corroborated by the study developed by Suzuki *et al* that aimed to investigate the effects of SGLT2i in glycemic control in a population of Japanese patients with T1DM in a real-world clinical setting.[13] There has been growing evidence that small increments in TIR measured by CGM may have beneficial effects in several diabetes complications,[14,15] thus emphasizing the overall benefits of using SGLT2i in selected patients with type 1 diabetes.

The improvement of %CV found in our study after the introduction of the SGLT2i is described in several other studies, being one of the major advantage of SGLT2 use in T1DM.[16,17] The %CV is correlated with risk of hypoglycemia[18] and, since the glucose-lowering effect of SGLT2i is insulin independent and glucose dependent, it is accompanied by reduced glucose variability.[2]

The GMI is the accepted method for using CGM-derived mean glucose to estimate lab-tested HbA1c. In the DEPICT 1 and 2 studies, the improvement in HbA1c with dapagliflozin was seen from week 4 of treatment and maintained to week 24. In a pooled analysis of the DEPICT studies, 39% and 11% of dapagliflozin 5 mg/day and placebo recipients achieved an HbA1c reduction of ≥ 0.5% without weight gain at week 24.[6,7] The significant reduction of GMI observed in this population (from 7.6% to 7%) reflects the positive effect of dapagliflozin in glycemic control, namely in the reduction of mean glucose levels.

Regarding glycemic excursion, although with no statistical significance, the introduction of dapagliflozin showed favorable results at lunch period, with levels that ranged from 7.2 mg/dL (±49.3) without SGLT2i to -4.5 mg/dL (±33.3), reflecting a mean lower glucose value after this meal with dapagliflozin.

Additionally, this study revealed a more pronounced effect of dapagliflozin at lunch time. In fact, when assessing glucose concentrations at pre- and post-lunch periods with and without dapagliflozin, a significant statistical difference was found. Furthermore, although with no statistical difference, glucose excursion was lower in this period with the SGLT2i in therapeutic regimen. On the contrary, at dinner time, glucose excursion with dapagliflozin did not improve and a statistical difference in glucose concentrations was only identified at pre-dinner time. Moreover, considering the difference between glucose levels after and before the introduction of dapagliflozin as a variable, the median was higher at post-lunch period (-35.45 mg/dL). The lowest median was observed at post-dinner period (-6.31 mg/dL). We do not have a definite explanation to the latter findings, but there are several possible explanations. All the patients included in this study took dapagliflozin after breakfast. As maximum plasma concentrations (C max) of this drug are usually achieved within 2 hours after administration in the fasted state,[19] this may have contributed to the better results obtained at lunch period due to better anti-hyperglycemic effect at lunch time. Furthermore, dapagliflozin and other SGLT2i have also been associated with increase in caloric intake, with some degree of carbohydrate craving, due to central nervous system activation, mainly in the left putamen. The higher plasmatic concentration at lunch time may also be associated with a higher intake of carbohydrates at lunch. A simpler explanation may be the intake of more carbohydrates or carbohydrates with a higher glycemic index at lunch time in comparison with dinner, leading to a more pronounced effect of dapagliflozin in the mitiga-

tion of glucose excursion at lunch time.[20,21]

The significant reduction of weight and BMI obtained in this population is recognized as one of the most beneficial reported effects in literature.[22] There was a mean reduction of 4.4 kg during follow-up, in a population whose baseline BMI was 30.79 kg/m2. Indeed, this drug has received approval for T1DM patients with BMI >27 kg/m^2. This BMI restriction reflects safety concerns around DKA risk in those with a lower BMI.[15,23] This weight reduction was similar in several other studies with either dapagliflozin or other SGLT2i.[3] The consistent reduction of body weight observed with dapagliflozin might also be important for some patients to limit later cardiovascular risk.[3]

In addition to body weight, several other clinical criteria have been pointed out as crucial to introduce this drug class in T1DM. Patients that require insulin dose injection of at least 0.5 units/kg of body weight per day were identified as candidates who mostly benefit from this therapeutic approach.[24] Our study population had a mean of total insulin dose per day of 0.71 units/kg of body weight per day, which is in accordance with the recommendations.

Other relevant finding was the significant reduction of TDD, basal dose and bolus dose after the introduction of dapagliflozin. These results were found in several other studies and may explain why the use of dapagliflozin as an adjuvant treatment allow better glycemic control without increasing the risk of hypoglycemia.[25] It may also contribute to the weight reduction observed after the introduction of the SGLT2 inhibitor.

In our study, eight patients were taking metformin in association with dapagliflozin. In the recent ADA-EASD consensus on the management of type 1 diabetes, the role of adjuvant therapies was comprehensively reviewed. Metformin is considered to have a minimal effect in glycaemia reduction (≈ 0,1% reduction in HbA1c) and a modest effect in weight, with no impact in insulin doses.[26] Considering the latter findings, we think that the overall glycemic benefit was due to dapagliflozin, despite a concomitant small effect of metformin may also have contributed to the final results.

One important aspect related with the use of SGLT2i in T1DM is tolerability and safety. Actually, the use of this drug class has potential associated adverse effects. Diabetic ketoacidosis (DKA) is an important complication of type 1 diabetes, and the risk is increased when SGLT inhibitors are used in this population. Furthermore, patients and healthcare providers must be aware that DKA associated with the use of these drugs may have an atypical presentation, as the glucose levels may be inappropriately normal – euglycemic DKA.[3] Therefore, it is recommended that the patients take part of an education program for DKA, including aspects like monitoring ketones, when to seek for medical help, when to stop the medication, and the need to avoid alcohol, illicit drugs or restrictive diets (low carbohydrate restriction or ketogenic diet).[17,27] The prevalence of DKA in the DEPICT and inTandem1 and inTandem2 studies ranged from 2% to 3% at week 24, being higher with higher doses of SGLT2i.[6,7,9] In our study, there were no episodes of DKA, probably because of the short time of follow-up and because the patients were strictly selected. Actually, T1DM patients that start SGLT2i in our center must be able to monitor blood glucose and capillary blood ketones regularly, and are educated on how to monitor rising levels of each, in addition to recognizing DKA. Also, the poorly compliant with insulin therapy and those who had episodes of DKA in previous month are not eligible. Equally, patients are advised to withdrawn SGLT2i during intercurrent illness, and increase frequency of glucose and ketone monitoring.

SGLT2i are also associated with an increased risk of genital mycotic infections, notably in premenopausal women. The increased risk of genital mycotic infections associated with SGLT2i has also been reported in a real-world setting study.[28] Although these infections have the potential to impact quality of life, the majority can be easily managed and do not necessitate dapagliflozin discontinuation. In our sample, only one female patient (5.88%) had a genital infection during the study period that was solved without the need to interrupt medication. This percentage is lower than the reported in literature (12% in DEPICT-1 study), probably because of the shorter follow-up.[6]

The withdrawn of type 1 diabetes indication for dapagliflozin by the pharmaceutical company has been a surprise. The company has argued that required changes to the product label would cause confusion among doctors when prescribing it for other conditions. However, UK and UE medicines regulators only advised that despite there being no new safety or efficacy concern, an inverted black triangle would need to be added to the label to signify the need of additional monitoring.[29]

The present study has some limitations. First, this was a single-arm retrospective and observational study, with no control group. Second, the number of patients included was small and the follow-up time was short, so the long-term effects could not be assessed. Also, other important factors, as the physical activity were not considered. Prospective studies evaluating long-term effects and safety of SGLT2 inhibitors in patients with type 1 diabetes are warranted.

Conclusion

The introduction of SGLT2i in this population improved glycemic control during the pre and postprandial periods. The maximal effect was observed in post-lunch period, possibly because of the therapeutic prescription schedule.

This reinforces the evidence that dapagliflozin could play a relevant role in the management of selected patients with T1DM, helping to address several important unmet treatment needs, including improved glycemic control with decreased glycemic variability, weight loss, and decrease in insulin dose.

Contributorship Statement / Declaração de Contribuição:

MAL: study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation.
BA: data collection, analysis and interpretation of results.
MM and LB: study conception and design, supervision.
IP: supervision.

All authors reviewed the results and approved the final version of the manuscript.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que

os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. Clin Diabetes. 2008;26:77-82.
2. Petrie JR. SGLT2 inhibitors and renal complications in type 1 diabetes. Lancet Diabetes Endocrinol. 2020;8:803-5. doi: 10.1016/S2213-8587(20)30311-9.
3. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (SGLT) Inhibitors. Diabetes Care. 2019;42:1147-54. doi: 10.2337/dc18-2316.
4. Song P, Onishi A, Koepsell H, Vallon V. Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. Expert Opin Ther Targets. 2016;20:1109-25. doi: 10.1517/14728222.2016.1168808.
5. Taylor SI, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. Lancet Diabetes Endocrinol. 2019;7:949-58. doi: 10.1016/S2213-8587(19)30154-8.
6. Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschope D, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5:864-76.
7. Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, et al. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial. Diabetes Care. 2018;41:1938-46.
8. Dandona P, Mathieu C, Phillip M, Hansen L, Tschope D, Thoren F, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-Week Study. Diabetes Care. 2018;41:2552-9. doi: 10.2337/dc18-1087.
9. Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care. 2018;41:1970-80. doi: 10.2337/dc18-0343.
10. Danne T, Cariou B, Banks P, Brandle M, Brath H, Franek E, et al. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. Diabetes Care. 2018;41:1981-90. doi: 10.2337/dc18-0342.
11. Rosenstock J, Marquard J, Laffel LM, Neubacher D, Kaspers S, Cherney DZ, et al. Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. Diabetes Care. 2018;41:2560-9. doi: 10.2337/dc18-1749.
12. Forxiga (dapagliflozin) 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus 2021 [accessed 2022-05-17]. Available from: https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-forxiga-dapagliflozin-5mg-should-no-longer-be-used_en.pdf .
13. Suzuki D, Yamada H, Yoshida M, Funazaki S, Amamoto M, Morimoto J, et al. Sodium-glucose cotransporter 2 inhibitors improved time-in-range without increasing hypoglycemia in Japanese patients with type 1 diabetes: A retrospective, single-center, pilot study. J Diabetes Investig. 2020;11:1230-7. doi: 10.1111/jdi.13240.
14. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42:1593-603. doi: 10.2337/dci19-0028.
15. Evans M, Hicks D, Patel D, Patel V, McEwan P, Dashora U. Optimising the Benefits of SGLT2 Inhibitors for Type 1 Diabetes. Diabetes Ther. 2020;11:37-52. doi: 10.1007/s13300-019-00728-6.
16. Paik J, Blair HA. Dapagliflozin: A Review in Type 1 Diabetes. Drugs. 2019;79:1877-84. doi: 10.1007/s40265-019-01213-x.
17. Garg SK, Peters AL, Buse JB, Danne T. Strategy for Mitigating DKA Risk in Patients with Type 1 Diabetes on Adjunctive Treatment with SGLT Inhibitors: A STICH Protocol. Diabetes Technol Ther. 2018;20:571-5. doi: 10.1089/dia.2018.0246.
18. Rodbard D. Glucose Variability: A Review of Clinical Applications and Research Developments. Diabetes Technol Ther. 2018;20:S25-S215. doi: 10.1089/dia.2018.0092.
19. Forxiga - Summary of Product Characteristics [accessed 22-02-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf .
20. Ferrannini E. Sodium-Glucose Co-transporters and Their Inhibition: Clinical Physiology. Cell Metab. 2017;26:27-38. doi: 10.1016/j.cmet.2017.04.011.
21. van Ruiten CC, Veltman DJ, Schrantee A, van Bloemendaal L, Barkhof F, Kramer MH, et al. Effects of Dapagliflozin and Combination Therapy With Exenatide on Food-Cue Induced Brain Activation in Patients With Type 2 Diabetes. J Clin Endocrinol Metab. 2022;107:e2590-9. doi: 10.1210/clinem/dgac043.
22. Riddle MC, Cefalu WT. SGLT inhibitors for type 1 diabetes: an obvious choice or too good to be true? Diabetes Care. 2018;41:2444-7. doi: 10.2337/dci18-0041.
23. Mathieu C, Dandona P, Birkenfeld AL, Hansen TK, Iqbal N, Xu J, et al. Benefit/risk profile of dapagliflozin 5 mg in the DEPICT-1 and -2 trials in individuals with type 1 diabetes and body mass index >/=27 kg/m(2). Diabetes Obes Metab. 2020;22:2151-60. doi: 10.1111/dom.14144.
24. Erskine D. Dapagliflozin for type 1 diabetes: ensuring benefits outweigh the risks. Drug Ther Bull. 2020;58:34. doi: 10.1136/dtb.2019.000081.
25. Mathieu C, Dandona P, Phillip M, Oron T, Lind M, Hansen L, et al. Glucose Variables in Type 1 Diabetes Studies With Dapagliflozin: Pooled Analysis of Continuous Glucose Monitoring Data From DEPICT-1 and -2. Diabetes Care. 2019;42:1081-7. doi: 10.2337/dc18-1983.
26. Holt RI, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2021;44:2589-625. doi: 10.1007/s00125-021-05568-3.
27. Goldenberg RM, Gilbert JD, Hramiak IM, Woo VC, Zinman B. Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: The STOP DKA Protocol. Diabetes Obes Metab. 2019;21:2192-202. doi: 10.1111/dom.13811.
28. Lega IC, Bronskill SE, Campitelli MA, Guan J, Stall NM, Lam K, et al. Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes. Diabetes Obes Metab. 2019;21:2394-404. doi: 10.1111/dom.13820.
29. Mahase E. Type 1 diabetes drug was withdrawn because of a “commercial conflict of interest,” charity argues. BMJ.2022;376:o373 doi: 10.1136/bmj.o373.