

Use of sodium-glucose cotransporter-2 inhibitors and urinary tract infections in type 2 diabetes patients: a systematic review

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SUMMARY

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are drugs that act by maintaining glycosuria. Recent studies have shown promising effects of these in the treatment of type 2 diabetes mellitus (DM2). However, there may be an increased risk of developing urinary tract infections (UTIs) in patients treated with these. Our study aims to analyze the association between the risk of UTI in patients treated with SGLT2i. A systematic review of the literature was carried out by randomized clinical trials, totalizing at the end of the selection 23 articles that were statistically evaluated. The incidence of UTI was generally demonstrated in articles and in different sub-groups: patients on SGLT2i monotherapy or on combination therapy; according to specific comorbidities of each sample or according to the drug used. They noticed an increase in the chance of UTI in the SGLT2i groups compared to the control groups on placebo or other oral antidiabetic agents. This increased chance was found predominantly with the use of Dapagliflozin, Canagliflozin, and Tofogliflozin, regardless of the dosing. Lastly, stands out that the dimension of UTI chances for DM2 patients who use SGLT2i remains to be more strictly determined.

KEYWORDS: Sodium-glucose transporter 2 antagonists/inhibitors. Diabetes mellitus, type 2. Urinary tract infections.

INTRODUCTION

The type 2 diabetes mellitus (DM2) accounts for approximately 90-95% of the diabetes cases worldwide. Its pathophysiology results from a combination of genetic, environmental and metabolic factors that initiate a state of hyperglycemia in the subject from peripheral insulin resistance and progressive failure of beta cells, resulting in decreased secretion of insulin by the pancreas.^{1,2}

The pharmacological therapies, although effective in the glycemic control, sometimes present

limitations that condition their use by patients. For this reason, new therapeutic agents are frequently researched. The sodium-glucose cotransporter-2 inhibitors (SGLT2i) propose an alternative therapy for DM2 based on an innovative mechanism substantiated on the renal importance of plasma glucose reabsorption.^{1,3}

The kidney reabsorbs the filtered glucose through sodium-glucose cotransporters (SGLT 1 and 2) located in the tubular epithelium. In the proximal contort-

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ed tubule, SGLT2 is responsible for the reabsorption of 90% of the filtered glucose. The action of SGLT2i is based on the inhibition of this transport, which reduces renal reabsorption of glucose and induces through the increase of glycosuria a decrease in the plasma glucose of the diabetic patient.^{3,4}

Some studies consider SGLT2i a promising therapeutic solution in the treatment of DM2. Given their mechanism of action independent of insulin, these can be used at any stage of the disease progression, with possible advantages such as decreased glycosylated hemoglobin, decreased fasting and postprandial glucose, weight reduction, blood pressure lowering and prevention of micro and macrovascular complications of diabetes, therefore improving the patient's quality of life. However, in these same studies that prove the efficacy of SGLT2i, cases of genito-urinary infection have also been observed in users; an effect that binds to glycosuria induced by SGLT2-1.¹⁻⁴

The aim of this article was to review the association between the use of SGLT2i in patients with DM2 and the development of urinary tract infections (UTI) to estimate and analyze the risk of this adverse effect on the therapeutic approach.

METHODS

A systematic computerized search was performed using the following databases: PubMed (Public MEDLINE - Medical Literature Analysis and Retrieval System Online - US National Library of Medicine National Institutes of Health), SciELO (Scientific Electronic Library Online) and Cochrane Library. Keywords included "sodium glucose cotransporter-2 inhibitors", "diabetes mellitus type 2" and "urinary tract infection". The following filters were also used in the search: "clinical trials", "randomized," and "human". The results of the search process are described below (Figure 1).

Study selection was completed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Initially, screening was conducted to exclude duplicate, irrelevant titles, and remaining abstracts. Subsequently, remaining full-text articles were independently screened by two authors for eligibility in the review. After, still as part of the eligibility process, some full-text articles were excluded if: they did not have statistical data on cases of UTI in their sample, did not give access to numbers and assessment of UTI cases, had inappropriate

size sample ($n < 100$), treatment duration with SGLT2i < 12 weeks (0,25 years), or did not mention the method for UTI detection.

At the end of the selection, 23 studies were included for the proposed systematic review. The data for analysis were arranged in tables in Excel (Microsoft, version 15.3) to produce the results. Afterward, the data obtained were transferred to RevMan (Cochrane Collaboration, version 5.3) for statistical evaluation. The measure of association was the odds ratio (OR) and confidence interval (CI) of 95%.

RESULTS

Twenty-three clinical trials, published between 2011 and 2016, were included and analyzed in the review. In these, the incidence of UTI was compared in patients with DM2 using SGLT2i *versus* the control group using a placebo or another antidiabetic of proven efficacy. The duration of SGLT2i treatment ranged from 0.5 to 2.6 years in the studies. In the selected articles, the following drugs used were: Dapagliflozin⁵⁻¹⁵, Canagliflozin¹⁶⁻²⁰, Empagliflozin²¹⁻²⁶, and Tofogliflozin²⁷. The characteristics of each study are in Table 1.

The profiles of the patients analyzed in the studies were those with DM2, using or not oral antidiabetic drugs or insulin, with or without associated comorbidities and of both genders. The total sample

FIGURE 1: FLOWCHART OF THE PROCESS FOR SYSTEMATIC REVIEW OF THE LITERATURE USING THE PRISMA (PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES) STATEMENT.

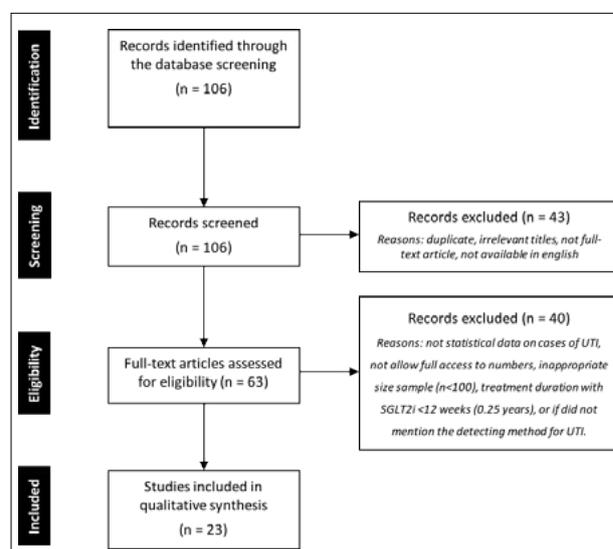


TABLE 1: CHARACTERISTICS OF THE STUDIES INCLUDED IN THE REVIEW.

Author	Year	Sample	SGLT2i analyzed	Sample characteristics	Treatment time
Cefalu et al	2013	1450	Canagliflozin	Metformin use	1 year
Inagaki et al	2014	272	Canagliflozin	With and without medication and inadequate glycemic control	0.5 year
Neal et al	2014	2072	Canagliflozin	Risk of cardiovascular disease and inadequate glycemic control	1 year
Nicolle et al	2012	451	Canagliflozin	Metformin use	0.25 year
Nicolle et al	2014	11752	Canagliflozin	With or without oral antidiabetic	2 years
Bailey et al	2014	167	Dapagliflozin	With and without medication and inadequate glycemic control	2.1 year
Bolinder et al	2012	182	Dapagliflozin	Female postmenopausal and man (30-75 years) on Metformin	0.5 year
Bolinder et al	2011	140	Dapagliflozin	Female on Metformin use	2.1 year
Del Prato et al	2015	814	Dapagliflozin	Metformin use	4.3 year
Jabbour et al	2014	451	Dapagliflozin	With and without medication and inadequate glycemic control	1 year
Ji et al	2014	393	Dapagliflozin	With and without medication and inadequate glycemic control	0.5 year
Leiter et al	2014	965	Dapagliflozin	With established cardiovascular disease	1.08 year
Nauk et al	2013	814	Dapagliflozin	Metformin associated or not to another oral antidiabetic	1 year
Rosenstock et al	2012	420	Dapagliflozin	Pioglitazona associated or not to another oral antidiabetic	1 year
Wilding et al	2012	808	Dapagliflozin	Obese in use of Insulin	1 year
Wilding et al	2014	808	Dapagliflozin	Use of up to 2 antidiabetics	2.1 year
Cherney et al	2016	3215	Empagliflozin	Micro or macroalbuminuria	1 year
Ferrannini et al	2013	659	Empagliflozin	Metformin use or not	0.25 year
Ridderstrale et al	2014	1545	Empagliflozin	Previous use of Metformin	2 years
Rosenstock et al	2014	563	Empagliflozin	Obese in use of Insulin associated or not with Metformin	1 year
Rosenstock et al	2013	495	Empagliflozin	Previous use of antidiabetic	0.25 year
Zinman et al	2015	7020	Empagliflozin	Cardiovascular disease without treatment with antidiabetic	2.6 years
Ikeda et al	2015	394	Tofogliflozin	With and without medication and inadequate glycemic control	0.25 year

for review was of 25,736 patients, and in the studies, the largest sample was 11,572 patients and the lowest 140, with a mean of 1,118 patients per study.

Together, the studies showed an increase in the chance of UTI in the SGLT2i group compared to the placebo (SGLT2i 2,133 of 23,594 [0.09%] *versus* placebo [0.08%], OD 1.18; 1.03–1.34; $p=0.02$), (Figure 2). The I^2 index of the Higgins Inconsistency Test in this analysis was 32%, indicating moderate heterogeneity of the sample. In addition, individual UTI trends in patients using SGLT2i were noted in the individual analyzes of the studies.¹⁻¹³ There was no evidence of publication bias observed by statistically constructed Funnel Plot.

In addition, we analyzed the incidence of UTI in different subgroups: in patients on SGLT2i monotherapy or in combination therapy, according to specific comorbidities of each sample, and according to each drug used.

Six articles analyzed patients on SGLT2i monotherapy^{5,9,15,17,21,22} and fourteen used patients on SGLT2i in combination with another oral antidiabetic agent^{6,8,9,11,14,16,20-25,27,28}; most of the associations were with Metformin. The odds of developing UTI in both monotherapy and combination therapy were higher

in the group using SGLT2i compared to the placebo (monotherapy: OD 1.24; 0.88–1.77; $p=0.22$; combined therapy: OD 1.24; 0.94–1.64; $p=0.13$).

Two studies analyzed the adverse effects of SGLT2i in patients on insulin therapy^{13,28}. Both used obese patients in the sample. SGLT2i was associated with insulin alone or with Metformin. For the combined use of insulin and Metformin, there was no difference in the chance of UTI in patients compared to the placebo (OD 1.0; 0.62–1.63; $p=0.48$)²⁸. For the association of SGLT2i with insulin, however, there was an increased chance of UTI in the experimental group (OD 1.70; 0.78–3.70; $p=0.48$)¹³. Statistical analysis of the studies together showed an increase in the chance of UTI with SGLT2i compared to the placebo (OD 1.19; 0.73–1.95; $p=0.48$).

In patients with an established cardiovascular disease or with risk factors for the development of this pathology, there was also an increased chance of UTI in the group using SGLT2i (OD 1.17; 0.81–1.69; $p=0.4$). Samples with these characteristics were selected in three studies^{10,18,26}. However, these showed marked heterogeneity among them ($I^2=72\%$).

One study observed the risk of UTI in 3215 patients with microalbuminuria or macroalbumin-

uria in use of SGLT2i²¹. In this study, there was no increased chance of UTI in patients on SGLT2i compared to the placebo (OD 0.93; 0.58–1.49; $p=0.75$).

Separate analysis of the drugs showed an increased chance of UTI in the groups using Dapagliflozin, Canagliflozin, and Tofogliflozin, regardless of the dose taken (OD 1.67; 1.35–2.08; $p<0.00001$; OD 1.15; 1.01–1.32; $p=0.04$; OD 1.63; 0.20–13.22; $p=0.65$, respectively). Only the Empagliflozin did not demonstrate an increased chance of UTI in comparison with the placebo (OD 0.95; 0.85–1.06; $p=0.39$) in the studies. However, one article included in the review showed that when Empagliflozin is used at a 50mg dose, there was an increased chance of developing UTI (OD 1.57; 0.25–9.69; $p=0.63$). However, in this same study, there was also an increased chance when the drug was used at lower doses²⁵. The characteristics of the drugs analysis on each study are shown in Figure 3.

DISCUSSION

Diabetic patients have an increased incidence of UTI compared to non-diabetic patients and present a increased severity of the disease. Diabetic women

present bacterial cystitis, asymptomatic bacteriuria, and symptomatic UTI associated with complications, more frequently than non-diabetic women, with an estimated risk four times higher. A possible explanation for this risk in diabetics is in the physiopathology, in which the high levels of glucose in the urine can promote bacterial growth. In addition, the restriction of the peripheral blood circulation caused by prolonged diabetes can cause abnormalities in the defense system, increase the probability of infections and gravity of this condition.^{29,30}

Glycosuria induced by SGLT2i, therefore, has been avidly researched in correlation with the infectious processes of the genito-urinary tract. Revision studies have shown an increase in the occurrence of genital infection in men and women using SGLT2i.^{29,30} Regarding UTI's, some recent reviews have shown, based on trial analysis, that patients treated with SGLT2i may have a slightly increased risk of developing UTI. The results demonstrated in our study corroborate such analyzes. We compared our study to the 2016 review conducted by Rizzi and Trevisan²⁹ that applied a similar methodology to evaluate, among other genito-urinary infections, UTI correlated with the use of SGLT2i in diabetic patients.

FIGURE 2: CHANCES OF URINARY TRACT INFECTION (REPRESENTED BY "EVENTS" IN THE CHART) IN PATIENTS WITH SGLT2I USE VERSUS THE CONTROL GROUP IN THE STUDIES INCLUDED. THE CHART ACCOMPANIES THE FORREST PLOT. ABBREVIATIONS: SGLT2I MEANS COTRANSPORTER-2 SODIUM-GLUCOSE INHIBITORS; CI, CONFIDENCE INTERVAL; I² CORRESPONDS TO THE INDEX OF THE HIGGINS INCONSISTENCY TEST IN THIS ANALYSIS.

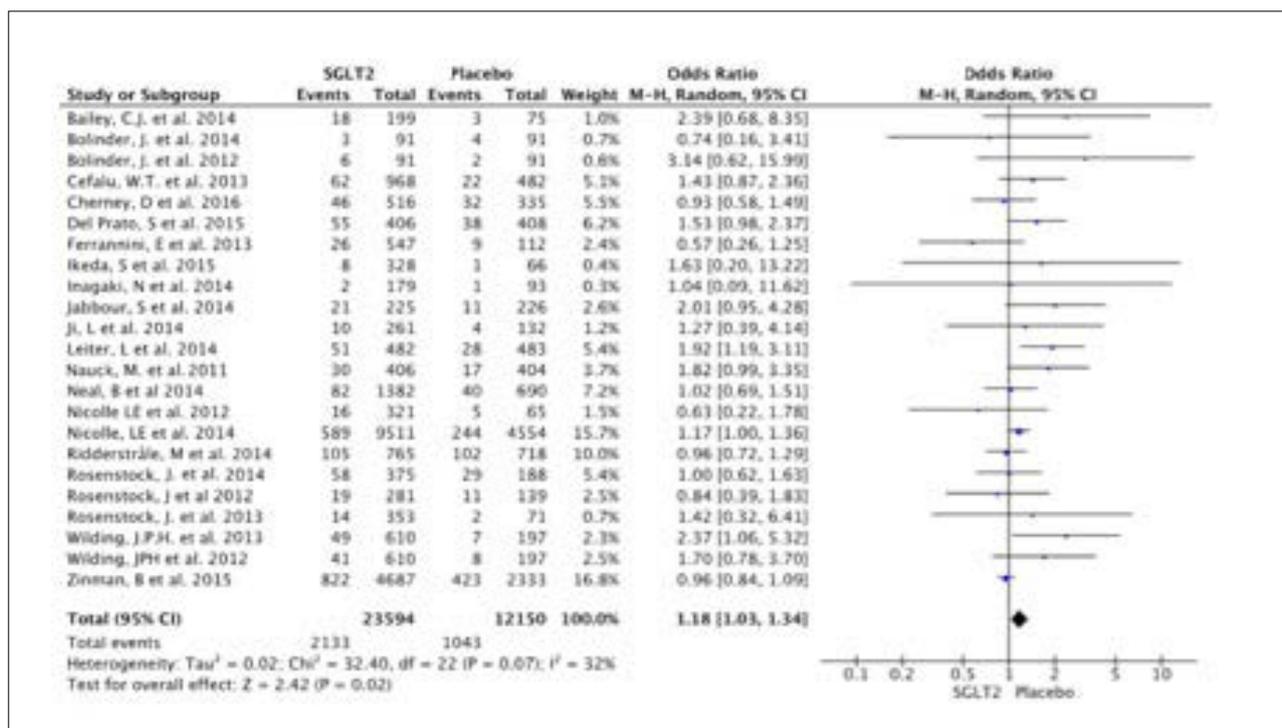
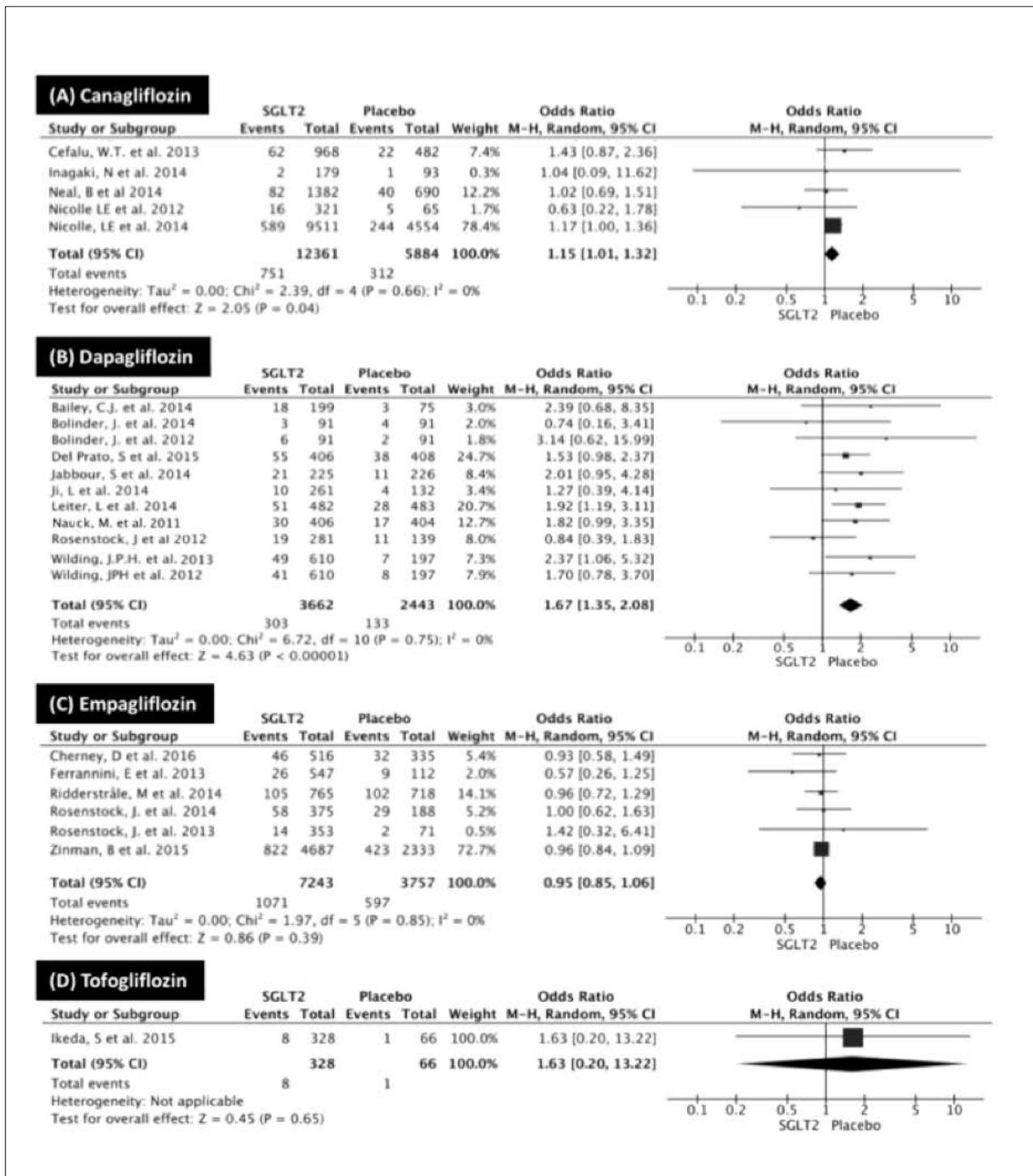


FIGURE 3: CHANCES OF URINARY TRACT INFECTION (REPRESENTED BY “EVENTS” IN THE CHART) IN PATIENTS WITH SGLT2I USE *VERSUS* A CONTROL GROUP, GROUPED ACCORDING TO THE DRUG ANALYZED IN EACH STUDY. THE CHARTS ACCOMPANY THE FORREST PLOTS CORRESPONDENCE IN (A) CANAGLIFLOZIN, (B) DAPAGLIFLOZIN, (C) EMPAGLIFLOZIN, AND (D) TOFOGLIFLOZIN. ABBREVIATIONS: SGLT2I MEANS COTRANSPORTER-2 SODIUM-GLUCOSE INHIBITORS; CI, CONFIDENCE INTERVAL; I² CORRESPONDS TO THE INDEX OF THE HIGGINS INCONSISTENCY TEST IN THIS ANALYSIS.



Studies matching Canagliflozin have shown that the chances of developing UTI are greater with the use of this inhibitor than it was with the placebo. There was a relationship with the dose of Canagliflozin, with a greater risk in patients who use 300mg

per day than in patients who use 100mg per day.³⁰ In our study, we observed an increased risk of UTI in patients who used Canagliflozin compared to the placebo, but we found no association with the dosing.

It has been shown that patients treated with Da-

pagliflozin may be at increased risk of UTI compared to the placebo group. The comparative difference was in the dose of the drug. While in the Rizzi and Trevisan²⁹ study the dose of 2,5mg Dapagliflozin per day was associated to a lower risk of UTI than the placebo, in our study, we found no significant relationship between the risk of UTI and the dose of Dapagliflozin.

As for Empagliflozin, studies have shown an increased probability of developing UTI in comparison with the placebo, except at a dose of 5mg per day, for which the chances of UTI were much lower than the placebo.³⁰ Our study showed that Empagliflozin does not present a risk of increased UTI when compared to the placebo at doses of 5, 10, or 25 mg per day. A single study in our sample experimented with 50mg of Empagliflozin and found an increase of UTI at all doses tested (10, 25, 50 mg/day).²⁵

As for Togliflozin, no review study evaluated its relationship with UTI. In our study, we included a single article focusing on this drug. It was found an elevated risk of developing UTI with SGLT2i in comparison with the placebo, although we did not see any dose relationship in the analyses.

Regarding the associations of SGLT2i with other oral antidiabetics in treatment, we found there is a superior chance of developing UTI in comparison with the placebo when the patient was in combination therapy.

There were no statistically significant results regarding the incidence of UTI among the different groups of patients analyzed: in monotherapy, in combined therapy, and insulin therapy; or in relation to associated clinical comorbidities, such as cardiovascular diseases and presence of renal injury (micro and macroalbuminuria).

Some limitations found limited the studies ana-

lyzed. The main limitation was in the diagnosis of UTI proposed in the methodology of the trials. We excluded the records that did not identify methods of detection of UTI in the methodology. Most studies used pre-specified queries, using lists of preferred terms from the Medical Dictionary for Regulatory Activity (MedDRA) to determine UTI in patients. Looking for evidence on the effectiveness and safety of the drugs, the trials did not focus on the procedures to detect UTI in their samples. Since there was a clinical identification through the symptoms reported by the patients during the period of treatment with SGLT2i, the possibility of these patients already having ITU prior to the start of the treatment has not been clearly excluded. This is an important fact since this comorbidity already has a high prevalence in diabetic patient.

CONCLUSIONS

Diabetic patients treated with SGLT2i had an increased chance of developing UTI compared to those who did not use it. This increased chance was found predominantly with the use of Dapagliflozin, Canagliflozin, and Tofogliflozin, regardless of the dosing. However, the dimension of UTI chances for the DM2 patients in use of these drugs still remains to be more strictly determined. The currently increased use of SGLT2i in clinical practice requires an analysis of urinary disorders, such as excluding the presence of UTI prior to the treatment, and the elaboration of more specific diagnostic methods for this pathology. These are imperative to determinate the long-term impact of increases in UTI episodes with SGLT2i use.

Conflict of Interest

The authors have no conflict on interest in this review.

RESUMO

Os inibidores do cotransportador de sódio-glicose do tipo 2 (SGLT2i) são medicamentos que atuam mantendo a glicosúria. Estudos recentes têm demonstrado efeitos promissores desses no tratamento de diabetes mellitus tipo 2 (DM2). No entanto, pode haver um risco aumentado de desenvolver infecções do trato urinário (UTI) em pacientes tratados com essa classe de medicação. Nosso estudo tem como objetivo analisar a associação entre o risco de desenvolver UTI em pacientes tratados com SGLT2i. Uma revisão sistemática da literatura foi realizada por ensaios clínicos randomizados, totalizando, ao final da seleção, 23 artigos que foram avaliados estatisticamente. A incidência de UTI foi demonstrada genericamente de acordo com os dados dos artigos e em diferentes subgrupos: pacientes em monoterapia com SGLT2i ou em terapia combinada, de acordo com as comorbidades específicas de cada amostra ou de acordo com a droga utilizada. Verificou-se um aumento na chance de UTI nos grupos SGLT2i em comparação com os grupos de controle em placebo ou outros agentes antidiabéticos orais. Essa chance aumentada foi encontrada predominantemente com uso de Dapagliflozina, Canagliflozina e Tofogliflozina, independentemente da dosagem. Por fim, ressaltou-se que as chances de UTI em pacientes com DM2 em uso de SGLT2i ainda precisam ser mais bem determinadas.

PALAVRAS-CHAVE: Inibidores/antagonistas do transportador 2 de glucose-sódio. Diabetes mellitus tipo 2. Infecções urinárias.

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