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REVIEW

Risk of urogenital infections in non-diabetic patients treated with sodium glucose transporter 2 (SGLT2) inhibitors. Systematic review and meta-analysis

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Summary

Although SGLT2 inhibitors have been initially employed in the treatment of type 2 diabetes, their clinical use was later extended to the treatment of other conditions such as heart failure, chronic kidney disease and obesity. In patients with type 2 diabetes, the administration of SGLT2 inhibitors has been associated with an increased incidence of urogenital infections, which may be linked to high glucose levels in the urine. The rate of urogenital side effects may be different in non-diabetic patients. The aim of this study was to review the risk of urogenital infections in non-diabetic patients taking SGLT2 inhibitors.

Materials and methods: We conducted a systematic review and meta-analysis by searching PubMed and EMBASE for randomized controlled trials (RCTs) reporting urogenital adverse effects in non-diabetic patients treated with SGLT2 inhibitors. Odds ratios for urogenital infections were calculated using random effect Mantel-Haenszel statistics.

Results: Out of 387 citations retrieved, 12 eligible RCTs were assessed for risk of bias and included in the meta-analysis. Compared to placebo, SGLT2 inhibitors were associated with increased odds of genital infections (OR 3.01, 95% CI: 1.93-4.68, 9 series, 7326 participants, $Z = 5.74$, $p < 0.0001$, $I^2 = 0\%$) as well as urinary tract infections (OR 1.33, 95% CI: 1.13-1.57, 9 series, 7326 participants, $Z = 4.05$, $p < 0.0001$, $I^2 = 0\%$). When four trials investigating the effects of SGLT2 inhibitors in populations including both diabetic and non-diabetic patients were considered, administration of SGLT2 inhibitors in diabetic patients was associated with significantly higher odds of genital infections but not urinary tract infections compared to patients without type 2 diabetes. In patients taking placebo, the odds for urinary tract infections were significantly increased in diabetic patients compared to non-diabetic patients.

Conclusions: The risk of genital infections is increased also in non-diabetic patients taking SGLT2 inhibitors although at a lesser extent that in diabetics. A careful assessment of the local anatomical conditions and of the history of previous urogenital infections is desirable to select those patients who need more intense follow-up, possibly combined with prophylactic measures of infections during treatment with SGLT2 inhibitors.

KEY WORDS: *Sodium glucose transporter 2 (SGLT2) inhibitors; Urinary tract infections; Genital infections; Candidiasis; Heart failure; Chronic kidney disease; Obesity.*

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Introduction

Sodium glucose transporter 2 (SGLT2) inhibitors have been recently introduced in the treatment of *type 2 diabetes* (T2DM).

The most frequently administered SGLT2 inhibitors are canagliflozin, dapagliflozin, and empagliflozin. The SGLT2 transporter is responsible for reabsorption of more than 90% of renal glucose from the urine filtered by renal glomeruli. In diabetic patients, administration of a SGLT2 inhibitor reduces the renal glucose threshold, resulting in glycosuria and in the lowering of plasma glucose levels. In patients with T2DM, administration of SGLT2 inhibitors as monotherapy or in combination with other antidiabetic agents was shown to lower HbA1C, to induce weight loss and to decrease blood pressure (1).

Somehow unexpectedly, SGLT2 inhibitors were found to be potentially useful in the management of heart failure (2). In addition, studies in patients with chronic kidney disease, showed that SGLT2 inhibitors reduced the risk of a decline of renal function or end-stage kidney disease regardless of the presence or diabetes (3, 4). Due to these favorable characteristics, SGLT 2 inhibitors are increasingly prescribed not only in patients with type 2 diabetes mellitus, but also in patients with cardiovascular and renal diseases. Interestingly, SGLT2 inhibitors have also proven to be effective in lowering body weight in obese patients without type 2 diabetes (5).

Although SGLT2 inhibitors are generally well tolerated, increased rates of genital and urinary tract infections have been reported (6, 7). The increased frequency of genital infections in diabetic patients treated with SGLT-2 inhibitors may be explained by high urinary glucose concentrations that can promote the growth of fungi on the surface of the genital mucous membranes.

However, the concentration of glucose in the urine of diabetic patients taking SGLT-2 inhibitors may be lower compared to the one measured in non-diabetic patients who are receiving SGLT-2 inhibitors for other conditions. For this reason, the risk of genital infections in patients taking SGLT-2 inhibitors for conditions other than type 2 diabetes may be different compared to patients with type 2 diabetes.

The aim of this systematic review and metanalysis was to evaluate the evidence describing the prevalence of genitourinary infections in non-diabetic patients receiving SGLT2 inhibitors for different conditions.

Materials and methods

Protocol and registration

The review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (8). The protocol for this review was registered on the PROSPERO platform (registration number: CRD42022375951).

Types of studies

We considered articles written in English, reporting *randomized controlled trials* (RCTs) evaluating the side effects of SGLT2 inhibitors, administered to diabetic or non-diabetic patients (i) for prevention of heart failure, (ii) for preserving renal function in end-stage kidney disease or (iii) for weight loss.

Types of patients

Participants of both sexes were involved irrespective of their age or ethnicity.

Types of interventions administered to patients

Patients on treatment with SGLT2 inhibitors or placebo were included in the present review.

Outcomes

The outcome considered for this review was the assessment of the prevalence of genital or urinary infections in subjects taking SGLT2 inhibitors compared to those not taking this treatment.

Search strategy

Two electronic databases (PubMed and EMBASE) were searched for records published up to January 31st, 2023. Broad search strings, based on MeSH terms, were used (e.g., [sodium glucose co-transporter-2 OR canagliflozin OR dapagliflozin OR empagliflozin) AND (urinary tract infections OR genital infections OR balanitis OR vulvovaginitis OR candidiasis OR Fournier gangrene]). Relevant data were also hand-searched by browsing reference lists of reviews and trial reports, or other sources. Duplicate references were excluded.

Data collection and analysis - selection of studies and data extraction

Title and abstract screening to exclude documents that did not meet the inclusion criteria was performed independently by four authors (two for each database). Selected titles were downloaded for full-text reading, for final inclusion and for extraction of relevant information. Controversies were resolved by one independent researcher. A PRISMA flow diagram was drawn to summarize the process of study selection. Data extraction was performed by four authors using a standardized form. The following data were extracted from each study report: author(s), publication year, study design, population, intervention, prevalence of genital and urinary infections. In case of missing or insufficient information, we considered the impact of missing data on the meta-analysis results.

Quality evaluation on methodology

Three authors independently performed the quality assessment by identifying potential biases using the Cochrane risk of bias tool (9). The following potential sources of bias were considered: randomization process (D1), deviations from the intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4) and selection of the reported result (D5).

Disagreements were resolved by discussion. Risk of bias was not used to exclude studies.

Statistical analysis

Statistical analysis was performed using the MetaEssentials-1 software (*Rotterdam School of Management, Erasmus University, The Netherlands*). Dichotomous data (presence/absence of urinary or genital stone disease) and number of subjects

were extracted to calculate *odds ratios* (OR), *confidence intervals* (CI) to odds-ratios, and Z statistics (*Random-effects model, Mantel-Haenszel method*).

Assessment of heterogeneity

Study heterogeneity was assessed by the I^2 statistic, reported with 95% CIs, and interpreted as of lesser importance ($I^2 \leq 40\%$), moderate ($I^2 = 30\%$-60%), substantial ($I^2 = 50\%$-90%) or considerable ($I^2 \geq 75\%$), according to Cochrane criteria. Sensitivity analysis was planned if considerable heterogeneity of pooled analyses including at least 4 studies was detected.

Assessment of reporting bias

Publication bias was assessed by funnel plot in the presence of at least 4 trials in each meta-analysis. If a potential bias was suspected by visual inspection of the plots, the Begg's and Egger's tests were used to test funnel plots symmetry and to confirm or exclude the presence of publication bias. The 'trim and fill' missing study imputation approach was applied to funnel plots; if missing studies were imputed by this procedure, adjusted overall effect sizes (odds ratios) were calculated and presented in the plots. Publication bias analysis was performed using the MetaEssentials-1 software (*Rotterdam School of Management, Erasmus University, The Netherlands*).

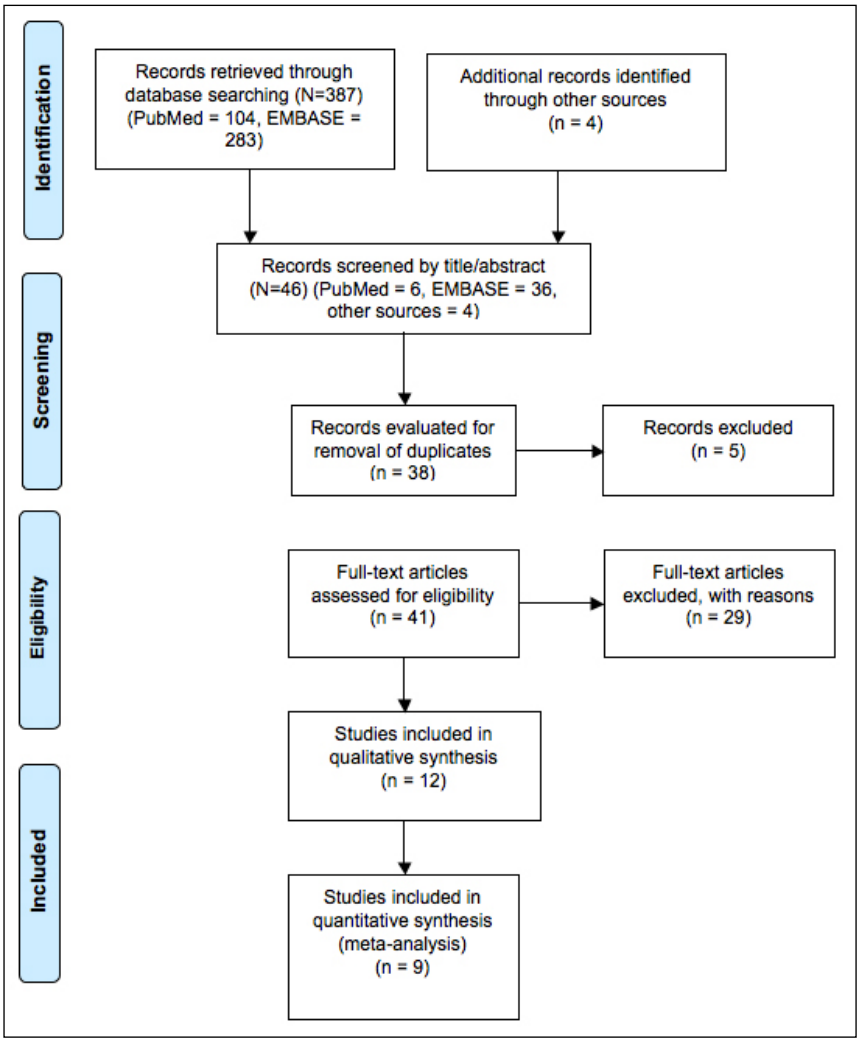
Results

Database search resulted in 387 retrieved records (Medline = 104, EMBASE = 283). Subsequent screening of title and abstract restricted the number of records to 42. Four additional studies were retrieved by hand-searching the references of selected studies. After removal of 5 duplicates, we considered 41 articles for full-text evaluation. Full-text evaluation resulted in the exclusion of 29 articles for the following reasons: one review article, 15 reports dealing only with type-2 diabetes patients, 2 articles reporting a comparison of SGLT2 inhibitors with other drugs, one letter to the Editor, 5 papers reporting the results presented in other included studies, 2 studies reporting short-term administration of SGLT2 inhibitors, one article dealing with cost-benefit of SGLT2 inhibitors treatment, 3 reports non presenting safety data.

The remaining 12 articles were included in the qualitative systematic review. Out of them, nine were included in the meta-analysis.

Figure 1.

PRISMA flow diagram of the record retrieval and selection process.



Included studies

Three studies included overweight or obese patients without DM type 2 receiving (i) canagliflozin or (ii) canagliflozin plus phentermine or (iii) dapagliflozin plus exenatide (10-12).

In the DIAMOND trial, dapagliflozin was administered to non-diabetic patients with chronic kidney disease and proteinuria (13).

In another study, the effect of dapagliflozin was evaluated in non-diabetic patients with heart failure and reduced ejection fraction (14).

In the remaining 7 studies, SGLT2 inhibitors were administered in populations that included both patients with type 2 diabetes and non-diabetic patients with heart failure (EMPEROR-Preserved, EMPEROR-Reduced, EMPERIAL, DAPA-HF, DELIVER) or chronic kidney disease (DAPA-CKD, EMPA-Kidney) (15-21).

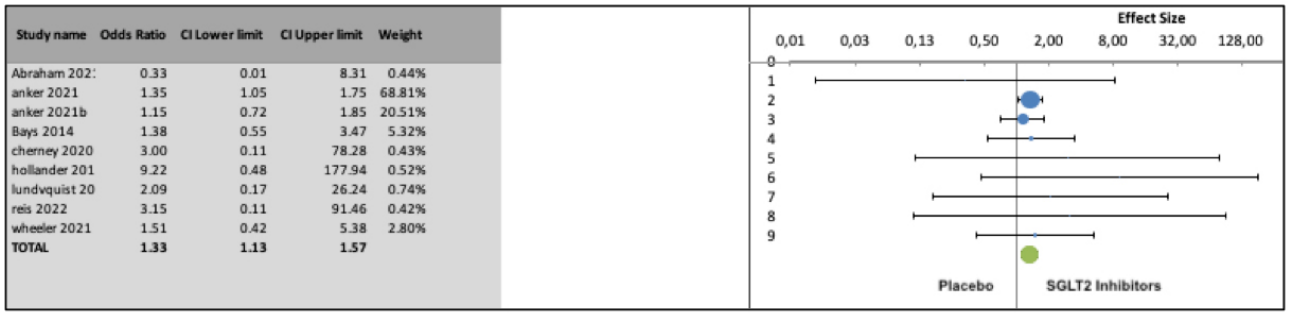
Data divided by diabetic status were available in two studies in the primary publication (16, 21). In two other studies we obtained from the Authors data presented according to diabetes status (22, 23).

Data extracted by the studies are presented in ***Supplementary Table 1***.

Quality assessment and risk of bias analysis

Of the 12 included studies, only one was classified as high risk (14), two studies were classified as having some

Figure 2.
Odds for urinary tract infections in non-diabetic patients taking SGLT2 inhibitors. Odds ratios of single studies and of the pooled analysis are presented. The values at the right of the no-effect bar show higher odds of infection in patients treated with SGLT2 inhibitors.



concerns (11, 16), and nine studies (10, 12, 13, 15, 17-21) were assessed as low risk of bias (***Supplementary Figure 1***). The study classified as high risk was assessed as having high risk of bias for the randomization process and presented some concerns with regard to deviations from intended intervention. The other two studies presented some concerns about randomization.

Meta-analysis

Meta-analysis was performed on 9 trials in which data were presented separately according to diabetes status.

Non-diabetic patients - Urinary tract infections - SGLT2 inhibitors vs placebo (9 studies)

There was a statistically significant difference in the odds of urinary tract infections in patients treated with SGLT2 inhibitors compared to placebo (OR 1.33, 95% CI: 1.13-1.57, 9 series,7326 participants, Z = 4.05, p < 0.0001, I^2 = 0%) (Figure 2). Although publication bias analysis did not detect a significant asymmetry of the funnel plot (p = 0.31, Egger's test; p = 0.14, Begg's test), the "*trim and fill*" strategy imputed three missing studies on the left side of the funnel plot (shown in the ***Supplementary Figure 2***); the resulting adjusted odds ratio was 1.30 (95%CI, 1.1-1.55).

Genital infections - SGLT2 inhibitors vs placebo

Similarly, a statistically significant difference in the odds of genital infections was observed when SGLT2 inhibitors were compared to placebo (OR 3.01, 95% CI: 1.93-4.68, 9 series, 7326 participants, Z = 5.74, p < 0.0001, I^2 = 0%) (Figure 3). Publication bias analysis did not detect a significant asymmetry of the funnel plot (p = 0.95, Egger's test; p = 0.29, Begg's test).

Non-diabetic vs diabetic patients - Urinary tract and genital infections - Treatment with SGLT2 inhibitors (4 studies)

In four studies comparing diabetic vs. non-diabetic patients taking SGLT2 inhibitors for heart failure or chronic kidney disease, we did not find a statistically significant difference of the odds for urinary tract infection (OR 1.34, 95% CI: 0.83-1.59, 4 series, 7317 participants, Z = 1.34,

Figure 3.
Odds for genital infections in non-diabetic patients taking SGLT2 inhibitors. Odds ratios of single studies and of the pooled analysis are presented. The values at the right of the no-effect bar show higher odds of infection in patients treated with SGLT2 inhibitors.

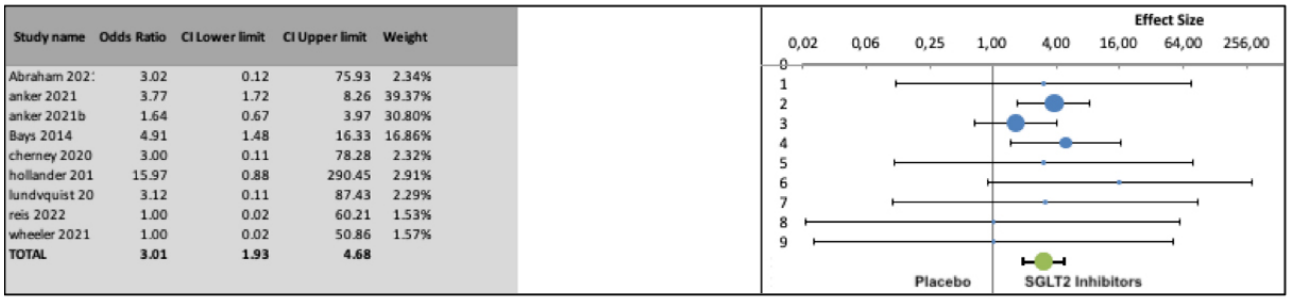


Figure 4.
Odds for urinary tract infection in diabetics vs non-diabetics taking SGLT2 inhibitors. Odds ratios of single studies and of the pooled analysis are presented. The values at the right of the no-effect bar show higher odds of infection in diabetic patients.

Figure 5.
Odds for genital infection in non-diabetics vs diabetics taking SGLT2 inhibitors. Odds ratios of single studies and of the pooled analysis are presented. The values at the right of the no-effect bar show higher odds of infection in diabetic patients.

Figure 6.
Odds for urinary tract infection in non-diabetics vs diabetics on placebo. Odds ratios of single studies and of the pooled analysis are presented. The values at the right of the no-effect bar show higher odds of infection in diabetic patients.

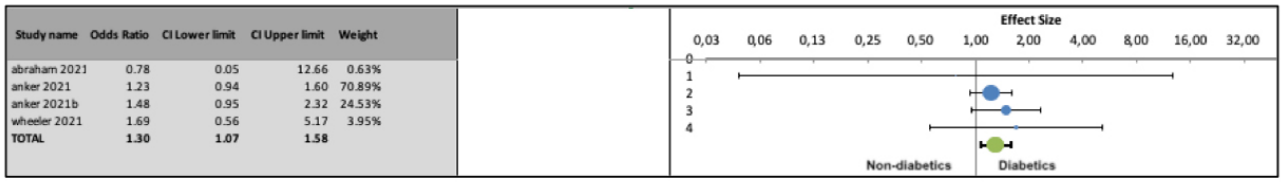
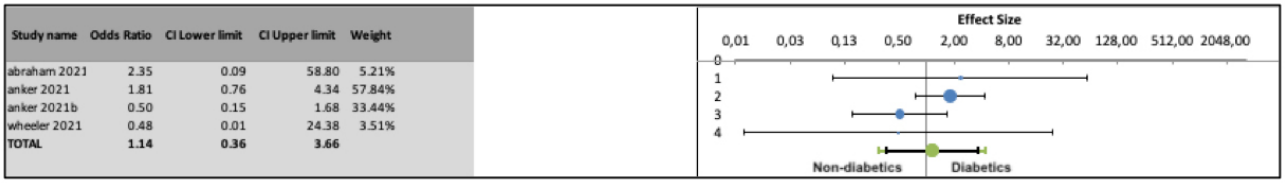


Figure 7.
Odds for genital infection in non-diabetics vs diabetics on placebo. Odds ratios of single studies and of the pooled analysis are presented. The values at the right of the no-effect bar show higher odds of infection in diabetic patients.



p = 0.091, I^2 = 0%) (Figure 4). However, significantly higher odds were found in diabetic patients for genital infections (OR 1.36, 95% CI: 1.07-1.72, 4 series, 7317 participants, Z = 4.08, p < 0.0001, I^2 = 0% (Figure 5). Although publication bias analysis of the odds for urinary tract infections did not detect a significant asymmetry of the funnel plot (p = 0.09, Egger's test; p = 0.49, Begg's test), the "*trim and fill*" strategy imputed two missing studies on the left side of the funnel plot (shown ***Supplementary Figure 2***); the resulting adjusted odds ratio was 1.11 (95%CI, 0.86-1.43). Funnel plots of the odds for genital infections showed asymmetry (p = 0.13, Egger's test; p = 0.042, Begg's test); two missing studies on the left side of the funnel plot were imputed by "*trim and fill*" (shown in the ***Supplementary material***); the resulting adjusted odds ratio is significant (1.33; 95%CI, 1.08-1.63).

Urinary tract and genital infections - Placebo (4 studies)
In the same four studies including diabetic vs. non-diabetic patients with heart failure or chronic kidney disease taking placebo, we found a statistically significant odds ratio for urinary tract infections (OR 1.30, 95% CI: 1.07-1.58, 4 series,7312 participants, Z = 4.29, p < 0.0001, I^2 = 0%) (Figure 6). Publication bias analysis did not detect a significant asymmetry of the funnel plot (p = 0.75, Egger's test; p = 0.99, Begg's test).
The odds for genital infection were not significantly higher in diabetic versus non-diabetic patients taking placebo (OR 1.14, 95% CI: 0.36-3.66, 4 series,7312 participants, Z = 0.37, p = 0.35, I^2 = 7.15%) (Figure 7).

Discussion

The effect of high urinary levels of glucose on the risk of urinary tract and genital infections is not fully investigated. Although it is well known that diabetes is an important risk factor for urinary tract infections (24), the possible role of high urine glucose concentrations in the pathogenesis of urinary tract infections has not been confirmed. The causes of the increased risk of urinary tract infections in diabetic patients has been attributed to multiple factors including alterations in the immune response, metabolic abnormalities and neurological and nephrological complications (25). In an *in-vitro* study, addition of glucose (up to a concentration of 1000 mg/dl) to urine enhanced the growth rate of pathogenic urinary isolates (26). In a clinical study higher levels of glucosuria were associated with higher rate of asymptomatic bacteriuria (27), although this finding was not confirmed by other Authors (28) and in a large series of women with either type 1 or type 2 diabetes, glucosuria was not associated with the development of symptomatic urinary tract infections (29).
Treatment with SGLT2 inhibitors of patients with type 2 diabetes was associated with a small increase in incidence of urinary tract infections, with no increase in serious or upper urinary tract infections (30).

The role of high urine glucose levels in the pathogenesis of genital mycotic infections in men and women is based on more robust considerations.
Candida species are polymorphic fungi that may colonize skin and mucosal surfaces acting as opportunistic pathogens (31, 32). The first phase of infection is adhesion of yeast forms to receptors on epithelial cells, which is mediated by adhesins and invasins (33) Subsequently, the filamentous hyphae are responsible for the formation of a biofilm on the superficial mucosa of the host (34). Colonization is favored by a carbohydrate-rich environment, which is a source of energy for producing biofilms that protect fungal cells from external agents (35-37).
The high incidence of genital infections in patients with uncontrolled glycemia can be attributed to different pathophysiological mechanisms (38). Infection can be favored by glucose, a viable nutrient for the growth of the fungi in the urine and in the secretions. Furthermore, in vitro studies have shown that high glucose levels facilitate the adhesion of *Candida* to cells through intercellular adhesion molecule 1 expression (39).
In addition, infections are more frequent in diabetic patients also due to compromised cellular immunity and to functional changes in polymorphonuclear cells, monocytes, and lymphocytes (40).
Meta-analyses including large populations of patients with type 2 diabetes treated with SGLT2 inhibitors demonstrated an up-to-four times increased risk of genital yeast infections for both genders in comparisons with placebo or other anti-hyperglycemic medications (41). According to some authors, the risk of *Candida* colonization and infection after SGLT2 inhibitors is even higher in real world practice (42).
Yokoyama et al. (42) found that among the patients who were initially negative for *Candida*, 37% converted to a positive culture after treatment with SGLT2 inhibitors and 16% developed symptomatic vulvovaginitis. This finding can be explained by urinary glucose excretion and the subsequent deposition of urine with high glucose content on the genital mucosa. On the other hand, the magnitude of the glucosuric effect of SGLT2 inhibitors in non-diabetic patients may be less pronounced than the one observed in diabetic patients. In a phase 1 study in healthy men, canagliflozin (i) decreased in a dose-dependent fashion the renal threshold for glucose, with maximal reduction to approximately 60 mg/dl, (ii) increased mean 24-h urinary glucose excretion and (iii) reduced postprandial plasma glucose (43). In another phase 1 study, canagliflozin significantly increased 24-h urinary glucose excretion in obese patients, but there were no significant changes in fasting plasma glucose and mean 24-h plasma glucose (44). In a phase 2b study in overweight and obese subjects without type 2 diabetes, mean 24-h urinary glucose excretion of 45-60 g was observed after canagliflozin administration (10). The effect of SGLT2 inhibitors on glucose excretion may be different in euglycemic subjects compared to diabetic patients because of SGLT1 activity. SGLT1 is a low-capacity, high-affinity transporter that mediates approximately 5% of glucose reabsorption in the S3 (distal) segment of the proximal tubule whereas SGLT2 is a high-capacity, low-affinity glucose transporter which is responsible for the reabsorption of approximately 90-95% of glucose in the S1 and S2 segments of the proximal tubule (45). Conversely, when SGLT2 is inhibited, a larger rate of glucose is reabsorbed by SGLT1, resulting in excretion of only 50-60% of filtered glucose (46). In fact, animal studies confirmed that the contribution of SGLT1 to renal glucose reabsorption is greater under lower glycemic conditions than under hyperglycemic conditions (47).
In our meta-analysis, the risk of genital infections and, to a lesser extent, of urinary tract infections was increased also in non-diabetic patients taking SGLT2 inhibitors.
Similarly, a previous meta-analysis showed no statistically significant different rates of genital and urinary tract infections in large series of patients taking SGLT2 inhibitors for treating type 2 diabetes or heart failure or chronic renal disease (48).
Our meta-analysis also demonstrated that odds of genital infection after taking SGLT2 inhibitors are higher in diabetic patients than in non-diabetics.
Diabetic status is therefore a risk factor for genital infections in patients taking SGLT2 inhibitors, although a primary care database study did not find an increased risk of infection in patients with higher HbA1c levels (49).
However, even non-diabetic patients treated with SGLT2 inhibitors must be carefully monitored for the onset of genital infections, especially in the presence of risk factors such as female gender, higher BMI and history of previous genital infection that are independently associated with risk for genital infection in patients treated with SGLT2 inhibitors (49). Similarly, male patients with foreskin phimosis may be at increased risk of developing a fungal infection because the moist, warm space underneath the foreskin promotes yeast growth, especially when hygiene is poor.

Conclusions

Genital infections in patients taking SGLT2 inhibitors are usually easily treated with appropriate antimycotic treatment. However, SGLT2 inhibitors may significantly increase the risk of serious infections. For this reason, it is advisable to adequately inform patients, who must be aware of the possible risks of genital infection. Increased hygiene measures should be recommended (e.g., frequent washing of the genital area, if possible after each urination). Subgroups of patients showing a markedly increased risk of genital infections when treated with SGLT2 inhibitors should be identified for closer follow up; prophylactic administration of antimycotic drugs to prevent candidiasis should be considered (50).
Circumcision surgery may be suggested in selected cases.

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