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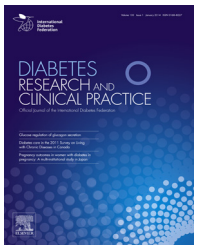

Genital and urinary tract infections in diabetes: Impact of pharmacologically-induced glucosuria

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ABSTRACT

Predisposition to genital infections and urinary tract infections (UTIs) in type 2 diabetes mellitus (T2DM) results from several factors such as glucosuria, adherence of bacteria to the uroepithelium and immune dysfunction. The tendency to develop these infections could be even higher in patients with T2DM treated with the emerging class of sodium–glucose cotransporter-2 (SGLT2) inhibitors. Studies have shown that pharmacologically-induced glucosuria with SGLT2 inhibitors raises the risk of developing genital infections and, to a relatively lesser extent, UTIs. However, a definitive dose relationship of the incidence of these infections with the SGLT2 doses is not evident in the existing data. Therefore, the precise role of glucosuria as a causative factor for these infections is yet to be fully elucidated.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a debilitating disease with multiple complications resulting from hyperglycaemia, inflammation, and possibly immune dysfunction. In addition to macro- and micro-vascular damage, T2DM is also associated with increased risks of asymptomatic bacteriuria (ASB), urinary tract infections (UTIs), and non-sexually transmitted genital infections (vulvovaginal infections and balanitis) [1,2]. ASB is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ colony-forming units per millilitre collected from a patient without symptoms of a UTI [3]. The presence of ASB (most commonly caused by *Escherichia coli* [*E. coli*] and *Klebsiella pneumoniae* [*K. pneumoniae*]) is a major risk factor for developing symptomatic UTI [4]. Patients with diabetes generally present with symptoms of UTIs similar to those reported in healthy controls. Complications of UTIs are also more common in patients with diabetes [5], and this population has an increased risk of acute upper UTI (pyelonephritis) requiring hospital admission [6]. Emphysematous pyelonephritis, a severe manifestation of this disease, is seen almost exclusively in patients with diabetes.

This review article aims to explore the relationship between diabetes and UTIs and genital infections, particularly in the context of emerging new therapies for T2DM that pharmacologically increase urinary glucose concentrations.

2. Search strategy

We conducted a search of the scientific literature to identify relevant studies in MEDLINE (1990–2012) using the search terms–type 2 diabetes, infections, urinary, vaginitis, balanitis and bacteriuria. We limited the literature searches to humans and English-language publications. The searches were supplemented by screening reference lists of included studies. Of the articles searched using the above strategy, 52 references were identified for inclusion in this review. Seven of these references examined prevalence and/or pathogenesis of ASB. Further, a total of 6 and 13 articles assessed incidence and/or pathogenesis of genital infections and of UTIs, respectively. The remaining references included data on events of genital infections and of UTIs reported in the SGLT-2 inhibitor class of glucose-lowering drugs.

3. Prevalence of ASB and associated risk factors in patients with T2DM

Various studies have estimated the prevalence of ASB or the incidence of UTIs in patients with diabetes [1,4,7]. A large majority of studies have shown a clear association between prevalence of ASB and diabetes, particularly in women [8]. However, ASB has not been shown to be associated with unfavourable long-term outcomes [9].

A systematic review and meta-analysis of data from 22 observational studies (16 cross-sectional and 5 follow-up studies) published between 1966 and 2007 provided a large volume of available data on the risk of ASB in patients with diabetes. All of the data in the current review for the prevalence of ASB come from the review of Renko et al. The results from this meta-analysis showed that ASB was present in 12.2% of patients with diabetes and 4.5% of patients in the healthy control group. The prevalence of ASB was higher in both women (14.2% vs. 5.1%; odds ratio (OR): 2.6 [1.6–4.1]) and men (2.3% vs. 0.8%; OR: 3.7 [1.3–10.2]) with diabetes compared with healthy controls [10]. Four studies in this meta-analysis assessed the effect of diabetes duration on the prevalence of ASB, and the results indicated that the mean diabetes duration was only very slightly longer in patients with ASB than in those without ASB (pooled difference of 0.17 years [95% confidence interval (CI):0.03–0.31]; $p = 0.01$). Furthermore, the mean glycated haemoglobin (HbA1c) levels were similar in patients with or without ASB (pooled difference 0.2% [−0.1, 0.5]; $p = 0.14$) suggesting that the increased prevalence of ASB may not be a direct consequence of poor glycaemic control of diabetes [10]. Supplementary Table 1 includes tabulated data for the risk of ASB in patients included in this systematic review and meta-analysis.

4. Incidence of UTIs and associated risk factors in patients with T2DM

A recent UK-based observational study in a primary care setting quantified the incidence of UTIs among patients with diabetes

(n = 135,920) and a 1:1 matched sample of patients without diabetes [11]. A nearly 60% increase in the risk of UTIs was observed among patients with T2DM (adjusted relative risk [RR] [95% CI] = 1.53 [1.46–1.59]); when stratified by both gender and age, the incidence of UTIs was highest in female patients with diabetes (1-year incidence/1000 patient years [PY] [95% CI] = 91.1 [84.3–99.4]) and lowest in male patients without diabetes (1-year incidence/1000 PY [95% CI] = 45.7 [44.0–47.5]). The study identified possible risk factors for UTIs as female gender, pregnancy, older age, UTIs in previous six months, prevalent diabetes, and poor glycaemic control (incidence [95% CI] in 'poorly controlled' DM [HbA1c >8.0% {64 mmol/mol} or switch to, or add-on of insulin] = 46.2/1000PY [43.8–48.7] vs. 39.4/1000PY [37.6–41.1] in 'fairly controlled' DM [no HbA1c measure >8.0% {64 mmol/mol} during the study period]).

A study in 1157 Indian patients with T2DM [12] showed an association between the percentage of patients with UTIs and duration of diabetes (41.8% [≤10 years] vs. 58.2% [≥10 years] of 146 men with UTIs [p = 0.07], and 42.4% [≤10 years] vs. 57.6% [≥10 years] of 349 women with UTIs [p = 0.007]), and poor glycaemic control (19.3% [HbA1c <8.0% {64 mmol/mol}], 13.2% [HbA1c range: 8.0–9.0% {64–75 mmol/mol}] and 64.9% [HbA1c ≥9.0% {75 mmol/mol}] in men [$p < 0.0001$], and 22%, 17.1% and 61.9%, respectively, in women [$p < 0.0001$]). The incidence of UTIs was significantly higher in women compared with men (47.9% vs. 34.1%, respectively, $p < 0.0001$). Perhaps due to cultural differences, reported rates of genital infections and UTIs may vary by geography. However, the risk factors are consistent, with increased incidences of these infections particularly seen in female patients with T2DM.

T2DM is also associated with more serious manifestations of UTIs. In one study, diabetes was estimated to increase the probability of acute pyelonephritis requiring hospital admission by 20–30 fold in patients under the age of 44 years and by three- to five-fold in patients over the age of 44 years [6]. Studies have also reported an increased incidence of bilateral kidney infection (identified by X-ray and CT scan) in patients with diabetes [13]. Furthermore, bacteraemia is more likely to occur from UTIs in patients with diabetes compared with the group without diabetes [14].

5. Pathophysiology of ASB and UTIs in patients with T2DM

There are several mechanisms that may explain the association between T2DM and UTIs. These include altered growth conditions (as a result of glucosuria and/or diabetes-associated bladder dysfunction), and altered pathogen–host interactions as a result of diabetes.

5.1. *Glucosuria*

One study reported that urine samples with glucose concentrations between 100 and 1000 mg/dL (i.e. equivalent to moderate to severe glucosuria) enabled significantly enhanced bacterial growth after 6 h, compared with normal urine ($p < 0.01$) [15]. Furthermore, a clinical study showed an association between glucosuria and ASB, where urinary glucose concentrations of 352.2 ± 458.8 and 62.4 ± 207.5 mg/dL ($p < 0.05$) were reported in patients with diabetes and ASB and those without ASB, respectively [16]. However, this pattern is not seen in all studies. For example, no association between glucosuria and ASB was noted in a large cohort of 636 women with diabetes, where 42% of the women without and 38% of the women with ASB had glucosuria (p = 0.4) [17]. It is possible that there is a threshold urinary glucose concentration above which ASB occurs more frequently. However, there are currently no in vivo data to quantify this. A study conducted in 348 women with T2DM reported various risk factors for the development of UTI in these women; the only significant factor was the presence of ASB at baseline. Glucosuria was not associated with the development of a symptomatic UTI in this study [18].

5.2. *Adherence of bacteria to the uroepithelium*

Increased adherence of bacteria to uroepithelial cells has been observed in patients with diabetes, particularly *E. coli* expressing type-1 fimbriae. This may play a role in the pathogenesis of UTIs and increased prevalence of bacteriuria in this population [19]. Adherence of *E. coli* with type 1 fimbriae to uroepithelial cells is higher in patients with poor glycaemic control. It has been suggested that the altered adherence may be due to a difference in the type 1 fimbriae receptors on uroepithelial cells of patients with and without diabetes. In particular, altered glycosylation of uroplakins, the major glycoproteins of urothelial apical plaques that line the bladder mucosa, has been observed in patients with diabetes [20].

5.3. *Immune dysfunction*

Hyperglycaemic environment has been observed to alter immune function in patients with diabetes. Several aspects of immunity including polymorphonuclear leukocyte function and adhesion, chemotaxis and phagocytosis may be affected [21]. This may contribute to the pathogenesis of urinary tract infections in patients with diabetes. Lower urinary concentrations of interleukin-8 and interleukin-6 (p = 0.1 and $p < 0.001$, respectively) in women with diabetes have been shown to correlate with a lower urinary leukocyte cell count, which may contribute to the increased incidence of UTIs in this patient group [22,23].

6. Epidemiology of genital infections and associated risk factors in patients with T2DM

Various studies have evaluated the prevalence of non-sexually-transmitted genital infections in diabetes [24]. The increased likelihood of genital infections in patients with T2DM is familiar to physicians and their patients. However, the exact nature of this condition deserves further discussion. A UK-based population study in a primary care setting evaluated the incidence of genital infections (vaginitis [n = 125,237] and balanitis [n = 146,603]) among patients with T2DM vs. patients without diabetes [25]. The results from this large population-based study indicated that patients with T2DM have an increased risk of developing genital infections (RR [95% CI] = 1.81 [1.64–2.00] in the vaginitis cohort and 2.85

[2.39–3.38] in the balanitis cohort), particularly in younger age groups (e.g. RR [95% CI] = 7.60 [3.57–16.20] in the balanitis age 18–39 years cohort), and in patients with poorly controlled diabetes (e.g. in patients receiving glucose-lowering therapy, in the first HbA1c quintile [mean HbA1c = 5.8 {40 mmol/mol}], adjusted RR [95% CI] for vaginitis = 0.63 [0.38–1.06]; whereas in the fifth HbA1c quintile [mean HbA1c = 9.7 {83 mmol/mol}], adjusted RR for vaginitis = 1.76 [1.3–2.38]).

A study conducted in 166 Indian women [26] included 78 patients with diabetes and 88 age- and BMI-matched controls. All subjects were assessed for symptoms and signs of vulvovaginal candidiasis (VVC), and a clinical diagnosis was established by fungal culture and direct microscopy. *Candida* species were isolated in 36 (46%) and 21 (23%) patients with and without diabetes, respectively ($p = 0.0025$). The most common species of candida isolated among patients with diabetes and VVC were *C. glabrata* (39%), *C. albicans* (25%) and *C. tropicalis* (17%). In contrast, *C. albicans*, *C. glabrata* and *C. hemulonii* comprised 30% each in the control group with none reporting *C. tropicalis* infection in this group. The mean HbA1c in patients with diabetes and VVC was significantly higher in comparison with those without infection (12.8% {116 mmol/mol} vs. 9.7% {83 mmol/mol}, respectively, $p = 0.001$), which supports a link between hyperglycaemic environment and an increased risk of VVC.

7. Pathophysiology of genital infections in patients with T2DM

It is well established that yeasts thrive in a sugar-rich environment, and therefore, it is logical to hypothesize that high glucose concentrations in patients with diabetes may be responsible for promoting the occurrence and recurrence of candidiasis. There are several potential mechanisms by which hyperglycaemia may facilitate vaginal candidal colonization. Hyperglycaemia impairs various aspects of host defense, including neutrophils and complement proteins, and also promotes the virulence of infecting organisms in patients with diabetes. One study examined neutrophil killing of *C. albicans* in the presence of increased concentrations of glucose [27]. Lucigenin-enhanced chemiluminescence showed that increases in glucose concentration led to increased aldose reductase activity, which was accompanied by sorbitol accumulation in neutrophils. As oxidative killing and sorbitol production are both NADPH-dependent, it was possible that competition for this electron donor is responsible for the inhibited neutrophil-mediated killing in patients with diabetes.

Studies have indicated that several organisms responsible for genital infections in patients with diabetes may possess unique mechanisms of virulence that flourish in the hyperglycaemic environment. *C. albicans* produces a glucose-inducible protein, which is structurally and functionally similar to a complement receptor CD11b/CD18, a protein found on mammalian phagocytes [28]. This protein mediates yeast adhesion to vaginal epithelium, and disrupts phagocytosis by the host. This mechanism may help to explain the increased adhesiveness of *C. albicans* to vaginal epithelial cells of women with diabetes observed in an in vitro study conducted using cells collected from a group of 347 women [29].

8. The effect of pharmacologically-induced glucosuria on genital and urinary tract infections

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are a new class of oral diabetes medication. These agents induce renal glucosuria by selectively targeting the renal SGLT2 transporter in patients with T2DM [30,31]. SGLT2 inhibitors in clinical development include dapagliflozin, canagliflozin, ipragliflozin, empagliflozin and tofogliflozin. Of these, dapagliflozin currently provides the large majority of information on SGLT2 inhibitors in the public domain.

The pharmacologically-induced increased urinary glucose concentration with this class of drugs might provide a favourable growth environment for otherwise commensal genital microorganisms, and could potentially increase the risk for vulvovaginitis and balanitis. The possibility of UTIs has also been raised as a concern with SGLT2 inhibitors. Data from controlled clinical trials with SGLT2 inhibitors may provide an opportunity to evaluate the association between elevated urinary glucose, and the risk for either genital infections or/and UTIs.

8.1. *Dapagliflozin*

Dapagliflozin dose-dependently induces glucosuria in patients with T2DM. Glucosuria was observed throughout a 24-h dosing interval with 5-, 25-, and 100-mg doses of dapagliflozin; urinary glucose excretion on day 1 was 45.2, 75.3, and 81.3 g/day, respectively, and after 2 weeks of once-daily treatment, it was 36.6, 70.1, and 69.9 g/day, respectively [30]. Long-term treatment with dapagliflozin 10 mg as add-on to metformin showed that increased urinary glucose excretion with dapagliflozin was maintained for up to 102 weeks. The mean change from baseline at week 102 in the urinary glucose-to-creatinine ratio was 31.8 g/g for dapagliflozin 10 mg dose vs. −0.21 for placebo [32].

Pooled data from 12 double-blind controlled clinical trials of dapagliflozin provided an opportunity to evaluate the effect of pharmacologically-induced glucosuria on the incidence of UTIs [33]. ASB was not evaluated in these studies. Patients with T2DM were treated with dapagliflozin (2.5–10 mg/day) for up to 24 weeks (3 studies–12 weeks; 9 studies–24 weeks). Dapagliflozin 10 mg was evaluated in all the studies that are presented, while dapagliflozin 5 mg was evaluated in 11 of the 12 studies. At 24 weeks, mean changes from baseline in urine glucose were −241, +2150 and +2592 mg/dL in the placebo, dapagliflozin 5 and 10 mg groups, respectively (baseline values were 511, 511 and 450 mg/dL, respectively).

8.1.1. *Confirmed UTIs in the pooled analysis of dapagliflozin clinical trials*

A rigorous effort was made to capture all signs, symptoms and events suggestive of UTIs. Symptoms spontaneously reported by study participants, as well as those reported following pro-active questioning of patients at each visit, were recorded throughout the dapagliflozin clinical program. The pro-active questioning included dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costovertebral angle tenderness, nausea,

Table 1 – Diagnosis of UTIs in dapagliflozin trials (up to 24 weeks).

	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg
Overall number of patients, *N*	1393	1145	1193
Patients with diagnosis of UTI, *n* (%)	52 (3.7)	65 (5.7)	51 (4.3)
Patients with history of recurrent UTI, *n* (%)	35 (2.5)	23 (2.0)	34 (2.8)
Patients with a prior history of recurrent UTI with clinical diagnoses of UTI, *n* (%)	6/35 (17.1)	4/23 (21.1)	6/34 (17.6)
Women			
N	677	581	598
Women with diagnosed UTI, *n* (%)	45/677 (6.6)	55/581 (9.5)	46/598 (7.7)
Men			
N	716	564	595
Men with diagnosed UTI, *n* (%)	3/716 (0.4)	6/564 (1.1)	4/595 (0.7)

vomiting, fever, chills, or sepsis. It was aimed to address the possibility of patients not recognizing certain symptoms as being relevant to the study. Investigators then performed urine cultures to confirm diagnosis in suspected cases, and all adverse events were reported. For safety signal detection, data were analysed according to a wide range of pre-specified preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), which included signs, symptoms, and abnormal laboratory findings suggestive of UTIs, as well as clinical diagnoses. These preferred terms were described as ''events suggestive of UTIs'' and a case-report questionnaire was completed by the investigator if any such term was reported. In a second analysis, 49 pre-specified, preferred terms that related to confirmed clinical diagnoses of UTIs were assessed.

The rates of clinically diagnosed UTIs were slightly higher in patients receiving dapagliflozin than receiving placebo. Clinically diagnosed UTIs were more frequent in women than men (Table 1) [33].

Prior history of recurrent UTIs was relatively uncommon (2–3%), but was associated with an increased incidence of episodes suggestive of UTIs irrespective of treatment group. Because history of UTI is a strong risk factor for UTI, the UTI incidence may be lower than expected in the dapagliflozin clinical trial programme. Most first events of UTIs occurred early in the course of treatment, and recurrent infection was uncommon. Most of the organisms identified were well-established causes of UTIs in the general population, e.g. *E. coli*, *Klebsiella* sp, and *Proteus* sp.

Most UTIs responded to treatment with standard antimicrobial medications (71% and 84% of episodes in the dapagliflozin 5 and 10 mg groups, respectively, and 89% of those in the placebo group). Pyelonephritis was infrequent in both treatment groups (0% and 0.1% in the dapagliflozin 5 and 10 mg groups, respectively, and 0.1% in the placebo group). Interruption or discontinuation of dapagliflozin as a result of events of UTIs was rare and occurred in 0.2–0.3% of patients in the dapagliflozin groups vs. 0.1% of patients in the placebo group. Supplementary Table 2 includes details on baseline characteristics, study duration and events of UTI in the individual dapagliflozin studies [31,34–43].

8.1.2. *Confirmed genital infections in the pooled analysis of dapagliflozin clinical trials*

As for UTIs, a rigorous effort was made to capture all signs, symptoms and events suggestive of vulvovaginitis and balanitis by recording not only spontaneous reports of symptoms, but also those reported during pro-active questioning of patients at each visit throughout the dapagliflozin clinical program. The pro-active questioning included itching, soreness or redness in the genital area and a change or increase in genital discharge. For safety signal detection, a broad range of preferred terms was used to capture symptoms, signs and abnormal laboratory findings suggestive of vulvovaginitis and balanitis, as well as specific diagnoses. These preferred terms were described as ''events suggestive of genital infections''. In a second analysis, 35 pre-specified, preferred terms related to clinical diagnoses were used to quantify diagnosed vulvovaginitis and balanitis, and the diagnosis was made based on physical examination, examination or culture of secretions, or by noting a therapeutic response to treatment of fungal or other vaginal pathogens, but physical examination for genital infections was not a protocol requirement.

The events of clinical diagnoses indicative of genital infections (not sexually transmitted diseases) were increased with dapagliflozin 5 and 10 mg doses as compared with placebo (with no clear dose relationship), and were more frequent in women than men (Table 2) [44].

Patients with a history of recurrent genital yeast infections were more likely to be diagnosed with genital infections compared with those without a prior history, irrespective of the treatment group (23.1% and 25% of patients in the dapagliflozin 5 and 10 mg groups, respectively, and 10% in the placebo group). Most first events of genital infections occurred early in the course of treatment (mostly in the first 24 weeks), and recurrent infections were uncommon. Most commonly reported events in women were vulvovaginal mycotic infection, vaginal infection, and vulvovaginal candiasis. In men, balanitis, fungal genital infection, and balanitis candida were most commonly reported.

The majority of patients responded to an initial standard course of treatment. Inadequate response to an initial course led to a need for an additional treatment in 6 (6.5%) and 3 (4.5%) patients receiving dapagliflozin 5 and 10 mg groups, respectively. Interruption or discontinuation of dapagliflozin as a result of events of genital infections was rare, and occurred in 0–0.2% of patients in the dapagliflozin groups vs. 0% of patients in the placebo group. Supplementary Table 2 includes details on baseline characteristics, study duration and events of genital infections in the individual dapagliflozin studies [31,34–43].

Table 2 – Diagnosis of genital infections in dapagliflozin trials (up to 24 weeks).

	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg
Overall number of patients, *N*	1393	1145	1193
Patients with diagnosis of genital infection, *n* (%)	12 (0.9)	65 (5.7)	57 (4.8)
Patients with history of recurrent genital infection, *n* (%)	10 (0.7)	13 (1.1)	12 (1.0)
Patients with a prior history of recurrent genital infection with clinical diagnoses of genital infection, *n* (%)	1/10 (10)	3/13 (23.1)	3/12 (25.0)
Women			
N	677	581	598
Women with diagnosed genital infection, *n* (%)	10 (1.5)	49 (8.4)	41 (6.9)
Men			
N	716	564	595
Men with diagnosed genital infection, *n* (%)	2 (0.3)	16 (2.8)	16 (2.7)

8.2. *Data on other SGLT2 inhibitors*

It is important to note that infections were not recorded using a consistent methodology in the clinical trials of different SGLT2 inhibitors, making it very difficult to compare infection rates between different agents.

8.2.1. *Canagliflozin*

A phase 2 study of canagliflozin evaluated the prevalence of bacteriuria and the frequency of AEs of UTIs in patients with T2DM [45]. A mid-stream, clean-catch urine specimen was used for dipstick analysis and culture at randomisation and at week 12. In addition, self-administered vaginal swabs were obtained at baseline and week 12, and at the time of a vulvovaginal AE. These swabs were cultured for *Candida* species. During the study, patients were asked open-ended questions about AEs. An AE of a UTI was assessed by the investigator. This included subjects with symptoms consistent with UTIs, whether or not a urine culture was reported, and also subjects with a positive urine culture identified, irrespective of symptoms. The prevalence of bacteriuria, *E. coli* bacteriuria, and candiduria was analysed for all patients with available urine culture data either at baseline or at week 12, and was stratified by gender. The initial prevalence of ASB was 6.4% and 6.5% in the pooled canagliflozin and placebo/sitagliptin (control) groups, respectively, and was higher in women. At week 12, no obvious differences in conversion from negative baseline urine bacterial culture to positive culture were observed in pooled canagliflozin vs. pooled sitagliptin/placebo group (4.8% vs. 3.7%, respectively; $p = 0.76$); corresponding with this, 14% and 25% of control and canagliflozin patients with initial prevalent bacteriuria remained bacteriuric ($p = 0.65$). The most common pathogens cultured were *E. coli* and *K. pneumoniae*. UTIs (both symptomatic and positive postbaseline urine culture reported as an AE) occurred in 21 (4.7%) patients: 16 (5.0%) in the pooled canagliflozin group and 5 (3.8%) in the pooled sitagliptin/placebo group (unadjusted OR = 1.31; 95% CI: 0.45–4.68). The adjusted and non-adjusted OR for UTIs with canagliflozin vs. sitagliptin/placebo were 2.39 (95% CI: 0.58–9.94) and 1.31 (95% CI: 0.45–4.68), respectively. All UTIs were mild or moderate, and none led to study discontinuation [45]. In conclusion, no differences in conversion from negative baseline to positive urine bacterial cultures and in the incidence of UTIs were observed in the pooled canagliflozin and sitagliptin/placebo groups at 12 weeks.

Further analysis of 215 women, from the phase 2 study discussed above, was conducted to evaluate vaginal candida colonization and symptomatic vulvovaginal AEs with canagliflozin treatment [46]. A clinical review of all AEs was performed, prior to unblinding, to identify all vulvovaginal AEs. All AEs were spontaneously reported and coded using the MedDRA dictionary. To be included in this analysis, the AE had to be symptomatic and either diagnosed by the investigator as an infection or treated as an infection with a medication. Vaginal swabs were collected from 198 women at baseline and at week 12, and during the study in case symptoms of VVC were noted. At baseline, 23/198 (12%) women had vaginal cultures positive for *Candida*. Thirty one percent of canagliflozin and 14% of placebo/sitagliptin patients converted from negative cultures at baseline to positive at week 12 (OR 2.8; 95% CI of difference: 1.0–7.3). Vulvovaginal AEs were noted in 16 (10%) and 2 (3%) patients in the canagliflozin groups and placebo/sitagliptin, respectively. Positive vaginal culture for *Candida* species at baseline was found as a risk factor for vulvovaginal AEs (OR 9.1; 95% CI: 2.4–34.0) [46]. Most of these infections were treated with topical or oral antifungal medications and resolved without study drug interruption.

Some of the recent canagliflozin studies have described the incidence of UTIs and genital tract infections in patients with T2DM over the longer-term. A large, randomised, double-blind, active-controlled Phase III study compared canagliflozin 100 and 300 mg with glimepiride in patients with T2DM ($N = 1450$) inadequately controlled with metformin. There were modest elevations in UTIs in the canagliflozin groups (6% each in the two canagliflozin groups) vs. comparator (5%) at 52 weeks. Higher rates of genital infections were noted in the canagliflozin 100 and 300 mg groups (7% and 8% in men; 11% and 14% in women) vs. comparator (1% in men and 2% in women) at 52 weeks [47]. Another randomised, double-blind, active-controlled, Phase 3 canagliflozin study in patients with T2DM ($N = 755$) inadequately controlled with metformin plus a sulfonylurea showed higher incidences of genital mycotic infections in patients treated with canagliflozin 300 mg (9.2% and 15.3% in men and women, respectively) vs. sitagliptin 100 mg (0.5% and 4.3% in men and women, respectively) at 52 weeks; however, these led to few study discontinuations. Incidences of UTIs were similar in canagliflozin (4.0%) and sitagliptin (5.6%) groups at 52 weeks [48].

In conclusion, more patients in the canagliflozin vs. placebo/sitagliptin group converted from negative cultures

for candida at baseline to positive at week 12. At 52 weeks, there were modest elevations in UTIs and higher rates of genital infections in the canagliflozin vs. sulphonylurea group. Similar incidences of UTIs and higher incidences of genital infections were noted in the canagliflozin vs. sitagliptin group at 52 weeks. Supplementary Table 3 provides further information on baseline characteristics, study duration and events of genital infections and of UTI in the individual canagliflozin studies.

8.2.2. *Empagliflozin*

A 12-week study in 408 treatment-naïve patients with poorly controlled T2DM reported UTIs in 1.2% of those receiving empagliflozin, and 1.2% and 1.3% of those taking placebo and metformin, respectively. Mycotic genital infections were reported in 0.8% and genital pruritus in 1.2% of patients receiving empagliflozin, and 0% for placebo and metformin [49]. A 12-week study in 495 patients with T2DM inadequately controlled with metformin found similar rates of UTIs in the empagliflozin (4.0%) and sitagliptin (4.2%) groups; however, slightly lower rates of UTIs were noted in the placebo group (2.8%). AEs of genital infections were reported in the empagliflozin (4.0%) and sitagliptin (2.8%) groups but not in the placebo group [50]. Supplementary Table 4 provides further information on baseline characteristics, study duration and events of genital infections and of UTI in the individual empagliflozin studies.

8.2.3. *Ipragliflozin*

A phase 2 study in patients with T2DM randomised to ipragliflozin or placebo reported UTIs in two female patients at days 9 and 14 of a 28-day study. There were no reports of any genital infections in the study [51]. Supplementary Table 4 provides further information on baseline characteristics, study duration and events of genital infections and of UTI in the ipragliflozin study.

9. Discussion and conclusions

Patients with T2DM are prone to UTIs and genital infections, and various studies suggest that factors such as glucosuria facilitating increased growth of bacteria, and increased adherence of bacteria to the uroepithelium, might be linked with the increased risk of these infections. However, the exact mechanism by which patients with T2DM experience a greater frequency of these infections is yet to be fully elucidated. This widely recognized association, together with an increase in urinary symptoms (particularly increased urinary volume and bladder dysfunction) in patients with diabetes, may in itself result in closer surveillance and hence, increased diagnosis of infections. Persons without diabetes may be less likely to seek medical advice for self-limiting infections, and the reported prevalence may not be comparable with that of a population with diabetes.

SGLT2 inhibitor-induced glucosuria likely plays a facilitating role in raising the risk of developing genital infections and, to a lesser extent, UTIs. Upper UTIs (pyelonephritis) is not increased with SGLT2 inhibitor treatment. The characteristics of the infections associated with SGLT2 inhibition are similar to those in any population with diabetes, as these infections respond to standard treatment and recur infrequently. In the case of genital infections, increased infection rates appear to be related to increased urinary glucose concentrations. However, this association is less clear with UTIs, where higher rates of infection were seen during treatment with the 5 mg dose of dapagliflozin vs. the 10 mg dose, despite lower levels of urinary glucose excretion.

Despite the increasing body of data, there remains some uncertainty around the true importance of UTIs and genital infections associated with SGLT2 inhibitor therapy. Due to their mechanism of action, SGLT2 inhibitors were expected to increase glucosuria, a well-recognized risk factor for genital infections. Because of this, infections have been closely monitored during the clinical development of this class of drugs. As a result, it is possible that events of UTIs were over-reported in the SGLT2 clinical trials, with any tendency towards over-reporting being similar in the placebo/control and intervention groups. In addition, SGLT2 inhibitors are associated with increased benign urinary symptoms (e.g. increased urinary output) due to osmotic diuresis. This potentially may have additionally increased the tendency towards diagnosis of infection in patients treated with SGLT2 inhibitors.

To conclude, data from clinical trials of SGLT2 inhibitors have shown that treatment of patients with T2DM is accompanied by an increased risk of developing genital infections and to a relatively lesser extent, UTIs. However, a definitive dose relationship of the incidence of these infections with the SGLT2 doses was not evident. Therefore, the precise role of glucosuria as a causative factor for these infections remains undetermined.

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Conflicts of interest statement

Dr Geerlings received honoraria for consulting from Bristol-Myers Squibb, AstraZeneca and Astellas. Dr Fonseca received honoraria for consulting and lectures from Glaxo Smith Kline, Takeda, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, Pamlabs, Xoma, Astra-Zeneca, Abbott and Bristol-Myers Squibb, and grants for research support (to Tulane) from Novo-Nordisk, Sanofi-Aventis, Eli Lilly, Abbott, Pamlabs and Reata. Dr Castro-Diaz has been speaker, consultant or investigator for Astellas, Takeda, American Medical System, Medtronic, Pfizer and Astra-Zeneca. Dr List is currently an employee and shareholder of Bristol-Myers Squibb. Dr Parikh is currently an employee of, and holds stocks and stock options in, AstraZeneca.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2013.12.052.

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