International Journal of Immunopathology & Pharmacology

*Letter to the Editor*

International Journal of Immunopathology and Pharmacology
Volume 33: 1–6

DOI: 10.1177/2058738419866582
journals.sagepub.com/home/iji
SAGE

# Urogenital infections in patients with diabetes mellitus: Beyond the conventional aspects

**Sandro La Vignera[1], Rosita A Condorelli[1], Rossella Cannarella[1], Filippo Giacone[1], Laura M Mongioi'[1], Laura Cimino[1], Giuseppe Defeudis[2], Rossella Mazzilli[3] and Aldo E Calogero[1]**

**Abstract**

Diabetes mellitus (DM) is a widespread disease in our country. Urogenital infections, including urinary tract infections, vaginitis, balanitis, balanoposthitis, and male accessory gland infections, show a higher risk of occurrence in patients with DM that non-diabetic subjects. Both non-drug-related and drug-related mechanisms are involved in their pathogenesis. These conditions may impact on glucose control and islets function in DM and more likely develop into adverse complications. A throughout microbial characterization, including the drug-sensitivity test, is required for a proper management. To reduce the risk of recurrence, combined treatment, including antibiotic, anti-inflammatory, and fibrinolytic molecules, should be prescribed also to the sexual partner. The choice of the antidiabetic drug to prescribe should take into consideration the presence of urogenital infections. In conclusion, urogenital infections may more likely lead to complication in diabetic than non-diabetic patients, affect fertility and glucose control. Therefore, they need proper management.

**Keywords**

balanitis, diabetes mellitus, MAGI, urogenital infections, UTIs, vaginitis

Date received: 24 April 2019; accepted: 5 July 2019

## Introduction

Diabetes mellitus (DM) is a vastly prevalent metabolic disorder with an increased risk of serious microvascular and macrovascular complications. Though less recognized, DM patients show a four-fold higher risk of common infections compared with non-diabetic patients, probably due to their abnormalities in immune function. Among infections, those of the genitourinary tract, including male accessory gland infection (MAGI), are more common and severe in diabetic patients than in general population.

The pathogenic mechanisms which are thought to be responsible for the susceptibility to urogenital infections are following summarized and a comprehensive overview of the main urogenital infections affecting patients with diabetes in the male and female gender is provided.

## Pathogenic mechanisms

Mechanisms playing a role in the development of urogenital infections in diabetic patients can be

[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[2]Unit of Endocrinology and Diabetes, Department of Medicine, Campus Bio-Medico University of Rome, Rome, Italy
[3]Andrology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

**Corresponding author:**
Sandro La Vignera, Department of Clinical and Experimental Medicine, University of Catania, Via S. Sofia 78, 95123 Catania, Italy.
Email: sandrolavignera@unict.it

classified into non-drug-related and drug-related ones. Non-drug-related mechanisms include autonomic neuropathy, glucose-dependent intercellular adhesion molecule-1 (ICAM-1) expression, and immune system competence. Concerning drug-related mechanisms, there are currently over 40 different drugs in 12 distinct classes approved in the United States to treat patients with type 2 DM. Except for Sodiumglucose co-transporter-2 inhibitors (SGLT-2i), among the new drugs for the treatment of DM, no risk of urogenital infections (UTIs) or genital infections has been found. SGLT-2i mainly includes Canagliflozin, Dapagliflozin, and Empagliflozin. Their efficacy in reducing hyperglycemia in patients with type 2 diabetes is well documented. Although SGLT-2i are generally well tolerated, they are associated with an increased risk of genital mycotic infections, as well as the potential risk for serious adverse events such as dehydration, development of diabetic ketoacidosis, serious urinary tract infections, and bone fractures (http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s015s019lbl.pdf. Accessed 20 August 2016; http://docs.boehringer-ingelheim.com/Prescribing%20Informati).

The increased risk of genital mycotic infections is likely to be related to the presence of urinary glucose, although no definitive dose relationship between incidence of infection and SGLT-2i treatment has been established to date. Genital mycotic infections associated with SGLT-2i more commonly occurred in females and in patients with a positive history for such infections (http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s015s019lbl.pdf. Accessed 20 August 2016; https://docs.boehringer ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf).

A meta-analytic study gathering together data on 7972 participants (5469 in Empagliflozin (EMPA) group and 2053 in the control group) from 15 studies reported the occurrence of UTI in 469 patients of the EMPA group (8.58%) and in 211 patients of the placebo one (10.28%). No significant difference was revealed both in overall and subgroup analysis according to concomitant therapy. Furthermore, genital infections were reported in 236 patients in the EMPA group (4.3%) and 33 patients in the placebo group (1.6%). A higher incidence of genital infection was revealed after EMPA treatment (relative risk 2.59, 95% confidence interval: 1.80–3.71, $P < 0.00001$). Subgroup analysis according to concomitant therapy revealed that only EMPA monotherapy, EMPA as add-on to pioglitazone or pioglitazone plus metformin and EMPA as add-on to insulin with or without other oral antidiabetic agent were associated with higher morbidity of genital infection. Subgroup analysis according to EMPA dosage demonstrated that both 10 and 25 mg EMPA were associated lower morbidity of hyperglycemia.[1]

## Urogenital infections in diabetic patients

Urogenital infections include UTIs in both genders, balanitis or balanoposthitis and MAGI in male and UTIs and vulvovaginitis in female patients. The main microorganisms identified in such conditions are listed in Table 1.

## Male genitourinary tract infections

### *Asymptomatic bacteriuria and symptomatic urinary tract infections*

Data from a systematic review and meta-analysis on 3579 diabetic patients and 2702 healthy controls reveal a threefold higher risk for asymptomatic bacteriuria (ASB) in patients compared to controls, with a higher prevalence in diabetic male patients compared to the healthy male controls (2.3% vs 0.8%; odds ratio 3.7). This prevalence was lower compared to that observed in female patients (12.9%). Similar findings have been recently reported for UTIs, as observed 3552 patients with type 2 DM.[2] More in detail, among 1783 male patients, only 68 were diagnosed for UTIs. On the contrary, among 1072 female ones, 341 had positive urine cultures.[6] This evidence suggests a lower incidence of UTIs in male compared to female patients.

### *Balanitis and balanoposthitis*

Balanitis is defined as the inflammation of the glans penis, posthitis as that of the prepuce. Since in uncircumcised men, both areas are concurrently affected, the term balanoposthitis is used. The risk of genital infections has been found much increased in diabetic than non-diabetic male patients, with a higher incidence in younger (18–39 years) and in uncircumcised patients. Despite several microorganism

**Table 1.** Microorganisms isolated in urogenital infections.

| | Microorganisms | References |
|---|---|---|
| UTIs | *Escherichia coli* (66%), *Klebsiella pneumonia* (5.9%), *Citrobacter freundii* (3.5%), *Proteus mirabilis* (2.5%), *Enterobacter* sp. (2.5%), *Acinetobacter* (2%), *Pseudomonas* sp. (1.5%), *Enterococcus* (5.9%), *Staphylococcus* (4.4%), *Streptococcus* sp. (1%), *Corynebacterium* (0.5%), *Candida albicans* (2%), *Candida parapsilosis* (1%), *Candida tropicalis* (0.5%) | He et al.[6] |
| Balanitis or balanoposthitis | *C. albicans*, Streptococci, Staphylococci, anaerobic bacteria, *Trichomonas vaginalis*, Herpes simplex | Lisboa et al.[3] |
| MAGI | *Enterobacteriaceae* (e.g. *E. coli, Klebsiella* species), *Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, C. albicans, T. vaginalis* | Calogero et al.[4] |
| Vaginitis | *Candida albicans, T. vaginalis, Prevotella* sp., *Mobiluncus* sp., *Gardnerella vaginalis, M. hominis, U. urealyticum* | Kalra and Kalra[5] |

MAGI: male accessory gland infection; UTI: urogenital infection.
Data on prevalence, where available, are showed in brackets.

may be implicated in the pathogenesis of balanitis (e.g. Streptococci, Staphylococci, anaerobic bacteria, *Trichomonas vaginalis*, Herpes simplex), the most common pathogen in diabetic patients is *Candida albicans*[3] (Table 1).

### *MAGI*

MAGI identifies a diagnostic category with a negative impact on the male reproductive function and fertility, mainly consisting in the inflammation and/or infection of epididymis, prostate and/or seminal vesicles. MAGI primarily has a chronic course and rarely cause obstruction of the seminal pathways. Furthermore, they can exhibit unpredictable intra-canalicular spread to one or more sexual accessory glands of the reproductive tract on one or both sides. Despite their high prevalence among men, although diabetic patients are exposed to infections of the genitourinary tract, few attention has been paid to MAGI in diabetic patients. Condorelli et al.[7] reported an increased frequency of MAGI (about 43%) among a cohort of 60 patients with type 2 diabetes (DM2), compared to age-matched non-diabetic infertile men and assumed that MAGI may represent a possible undiagnosed complication of this condition. La Vignera et al.[8] also reported differential ultrasound characterizations (lack of reduction of inter-parietal thickness after ejaculation and alteration of the relationship between glandular fund and body) of the seminal vesicles in these patients, particularly among those with diabetic autonomic neuropathy (DAN), suggestive of functional atony.[9] Specifically, patients with symptoms of DAN exhibited higher frequencies of MAGI compared with DM2 patients without symptoms. Furthermore, the frequencies of ultrasound findings of prostato-vesiculo-epididymitis (having a more extensive anatomical involvement) were higher in the group with symptoms possibly reflecting DAN than in the group without them. Moreover, symptomatic patients showed a worse semen quality compared to those without symptoms. Specifically, seminal lymphocyte concentration was significantly higher in patients with symptoms possibly reflecting DAN than the others. Finally, sperm densities, semen lymphocytes concentrations, ejaculate volumes, and fructose levels were significantly different between DM2 patients with MAGI with or without symptoms possibly reflecting DAN, negatively impacting on fertility.[2]

Despite several microorganisms have been identified in patients with MAGI, such as *Enterobacteriaceae* (e.g. *Escherichia coli, Klebsiella* species), *Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, C. albicans, T. vaginalis*[4] (Table 1), no study evaluated whether a different microbial pattern may occur in DM patients so far. These microorganism can alter the secretory function of the epididymis, seminal vesicles, and prostate reducing the antioxidant properties or scavenging role of the seminal plasma.

## Female genitourinary tract infections

### *ASB and symptomatic urinary tract infections*

The urinary tract is the most prevalent site of infection in female diabetes patients, being ASB and symptomatic UTIs frequently observed in these patients. The prevalence of ASB has been reported to range between 8% and 26% in diabetic female patients. The clinical significance of

ASB is uncertain. A clear association between higher glycated hemoglobin levels and ASB risk was found only in one study, despite longer duration of diabetes, neuropathy, and heart disease were more frequently observed among patients with bacteriuria. The most commonly isolated microorganism is *E. coli* (65%), showing multi-drug resistance in one half of cases[6] and meropenem sensitivity in the remaining ones, followed by *Klebsiella* (12%) and *Enterococcus* (10%) (Table 1). Interestingly, neither ASB nor UTIs seem to show a higher prevalence in diabetic pregnant patients compared to healthy pregnant women and, therefore, the routinely research of ASB in diabetic pregnant women has been discouraged.

### *Vulvovaginitis*

Vulvovaginitis is common among diabetic patients.[5] Patients with diabetes, especially those with poorly controlled glycaemia, are prone to develop genital mycotic infections. *C. albicans* is the dominant cause of vulvovaginal infections in women with diabetes. Genetics, pregnancy, estrogen/oral contraceptive use, and select sexual behaviors (e.g. orogenital sex) have been identified as the main risk factors for vaginitis in diabetic patients. The adhesion of Candida to the epithelium has been shown to be ICAM-1 dependent. ICAM-1 expression is in turn influenced by glucose concentration. This may explain the higher incidence of vaginal candidiasis in patients compared to controls. Consisting with these findings, this increased incidence has been observed after treatment with SGLT-2i.

Interestingly, vulvovaginal candidiasis has been recently found with a higher frequency in patients with gestational diabetes mellitus (GDM) compared to healthy pregnant women (22.6% vs 9.7%; $P < 0.001$) in a prospective Chinese study. Candidias is known to affect the pregnancy outcome.

Abnormal vaginal flora (mainly consisting of different *Lactobacillus* species) has been found in GDM patients. It may induce anaerobic bacterial overgrowth, including *Prevotella* sp., *Mobiluncus* sp., *Gardnerella vaginalis, Mycoplasma*, and *Ureaplasma*, leading to bacterial vaginosis. Besides lack of vaginal *Lactobacilli*, multiple sexual partners, sexually transmitted disease, douching are associated with the risk of developing bacterial vaginosis. In addition, abnormal vaginal flora has been associated with adverse pregnancy outcomes (premature rupture of the membranes, premature delivery, chorioamnionitis, puerperal infections). Hence, both vaginal candidiasis and bacterial vaginosis should deserve proper investigation in GDM patients.

## Clinical management

Urogenital infections, including MAGI, need proper management in diabetic patients. Indeed, they may more likely let to complication in diabetic than non-diabetic patients. In agreement, UTI is more frequently complicated by bacteremia, renal abscesses, renal papillary necrosis, emphysematous pyelonephritis, and sepsis in diabetic patients. Accordingly, albuminuria (a marker of diabetic nephropathy) and symptomatic UTI more commonly occurred among diabetic patients with ASB. In addition, their occurrence may negatively impact on pregnancy outcome in GDM, as previously discussed.

Post marketing reports of cases of potentially fatal uro-sepsis and pyelonephritis that developed from UTIs in patients receiving SGLT-2i have led to a warning from the Food and Drug Administration (FDA) (December 2015) about the possibility of severe urinary tract infection and pyelonephritis with these agents (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM475487.pdf). On 29 August 2018, the FDA issued a new warning about Fournier's gangrene, a severe polymicrobial infection resulting in necrosis of perineal and genital fasciae, between 12 people who had been treated with an SGLT-2i between 2013 and 2018. In addition, a retrospective study on 3652 type 2 diabetes mellitus patients has recently showed a negative impact of UTIs on the islet function and metabolic control.[6]

In the light of such evidence, clinicians should accurately check for urogenital infections in diabetic patients and personalize the choice of antidiabetic therapy based on the specific characteristics of the patient, including the occurrence of signs and symptoms of UTIs and genital infections and treat such infections promptly, if indicated.

### *Management of urogenital tract infections*

Prior to antibiotic therapy, a proper microbial investigation with the research of the more common pathogens (Table 1) and the drug-sensitivity

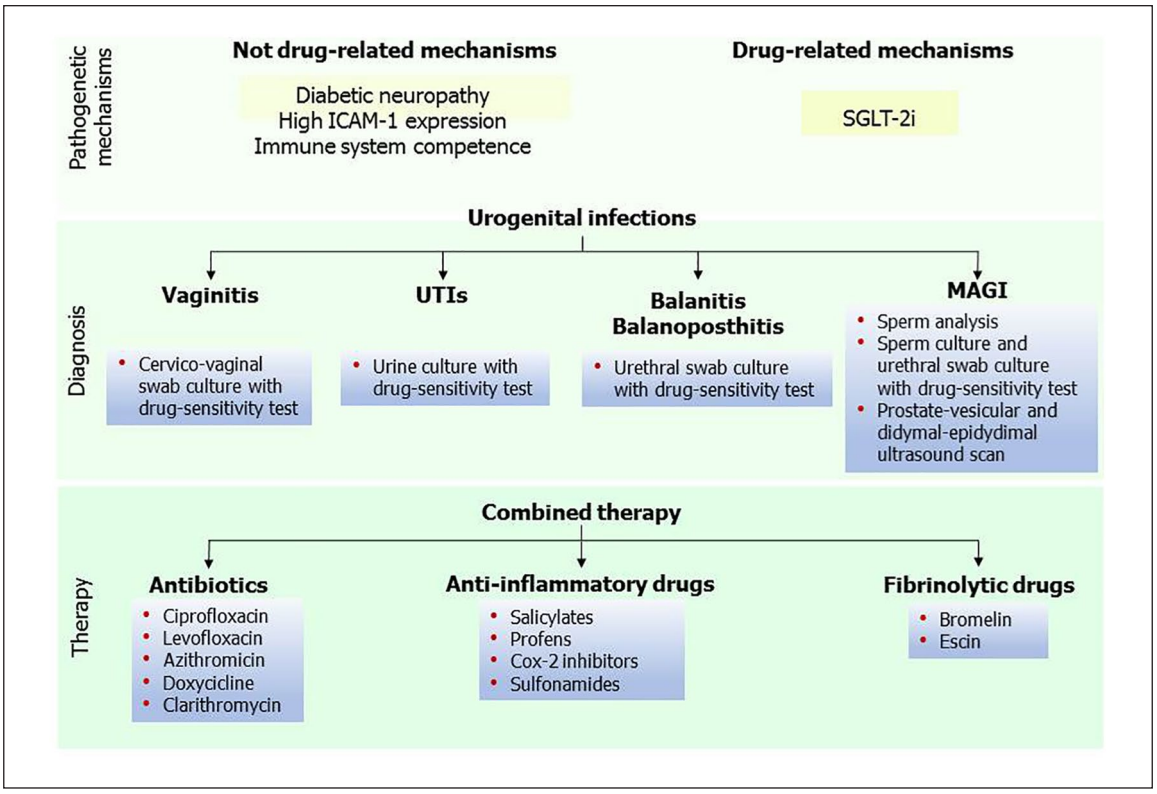


**Figure 1.** Management of urogenital tract infections. Both non-drug-related and drug-related mechanisms occur in the pathogenesis of urogenital infections in diabetic patients. Proper management needs a deepened microbial characterization, which include drug-sensitivity test. = Combined therapy costs of antibiotics, anti-inflammatory, and fibrinolytic drugs. Treatment should also be prescribed to the partner to avoid recurrence.

test is required, due to multi-drug resistance issues.[6] In greater details, diagnostic strategies of urogenital tract infections include the cervico-vaginal swab culture or the urine culture with drug-sensitivity test when vaginitis or UTIs are suspected, respectively. In case of balanitis or balanoposthitis, the urethral swab culture should be requested. Finally, proper diagnosis of MAGI require the sperm analysis, sperm culture, and urethral swab culture with drug-sensitivity test and the prostate–vesicular and didymal–epididymal ultrasound scan. With the advantages coming from proteomic analysis, new molecular markers may be added in the next future in the diagnostic panel of genitourinary infections.[10]

Treatment options include antibiotics, anti-inflammatory, and/or fibrinolytic drugs. The choice of the specific antibiotic treatment should be driven by the result of the drug-sensitivity test and the patient clinical feature (e.g. drug allergy, renal insufficiency). In coupled patients having sexual intercourse, the treatment should be prescribed to both members of the couple to prevent the risk of recurrence. Furthermore, since urogenital infections impact on fertility,[10] the clinical management should include the counseling for fertility issues. Anti-inflammatory therapy has been recognized to play a role in the treatment of urogenital tract infection, and to improve sperm parameters in male patients, mainly by reducing reactive oxygen species-induced damage.[11] Finally, fibrinolytic drugs such as bromelin or escin have been proven to improve antibiotic efficacy enhancing the penetrance of antibiotics in prostate biofilm.[12] A flow chart of the management of urogenital infections is given in Figure 1.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iDs

Sandro La Vignera https://orcid.org/0000-0002-7113-2372

Laura M Mongioi' https://orcid.org/0000-0003-2341-0996

Aldo E Calogero https://orcid.org/0000-0001-6950-335X


## References


1. Zhang YJ, Han SL, Sun XF, et al. (2018) Efficacy and safety of empagliflozin for type 2 diabetes mellitus: Meta-analysis of randomized controlled trials. *Medicine* 97(43): e12843.
2. Condorelli RA, LaVignera S, Mongioi LM, et al. (2018) Diabetes mellitus and infertility: Different pathophysiological effects in type 1 and type 2 on sperm function. *Frontiers in Endocrinology* 9: 268.
3. Lisboa C, Ferreira A, Resende C, et al. (2009) Infectious balanoposthitis: Management, clinical and laboratory features. *International Journal of Dermatology* 48(2): 121–124.
4. Calogero AE, Duca Y, Condorelli RA, et al. (2017) Male accessory gland inflammation, infertility, and sexual dysfunctions: A practical approach to diagnosis and therapy. *Andrology* 5(6): 1064–1072.
5. Kalra B and Kalra S (2017) Vulvovaginitis and diabetes. *Journal of the Pakistan Medical Association* 67(1): 143–145.
6. He K, Hu Y, Shi JC, et al. (2018) Prevalence, risk factors and microorganisms of urinary tract infections in patients with type 2 diabetes mellitus: A retrospective study in China. *Therapeutics and Clinical Risk Management* 14: 403–408.
7. Condorelli RA, Calogero AE, Vicari E, et al. (2013) Prevalence of MAGI in patients with type 2 diabetes mellitus. *Journal of Endocrinological Investigation* 36: 770–774.
8. La Vignera S, Condorelli RA, Vicari E, et al. (2011) Seminal vesicles and diabetic neuropathy: Ultrasound evaluation. *Asian Journal of Andrology* 13(6): 872–876.
9. La Vignera S, Vicari E, Condorelli RA, et al. (2011) Ultrasound characterization of the seminal vesicles in infertile patients with type 2 diabetes mellitus. *European Journal of Radiology* 80(2): e64–e67.
10. La Vignera S, Vicari E, Condorelli RA, et al. (2011) Male accessory gland infection and sperm parameters. *International Journal of Andrology* 34(5 Pt 2): e330–e347.
11. La Vignera S, Cannarella R, Condorelli RA, et al. (2018) The advantages of proteomic investigation in the management of male accessory gland infection: A response to Grande et al. *American Journal of Reproductive Immunology* 80(6): e13063.
12. Cannarella R, Calogero AE, Condorelli RA, et al. (2019) Non-hormonal treatment for male infertility: The potential role of *Serenoa repens*, selenium and lycopene. *European Review for Medical and Pharmacological Sciences* 23(7): 3112–3120.