REVIEW

Genitourinary infections in diabetic patients in the new era of diabetes therapy with sodium-glucose cotransporter-2 inhibitors

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Abstract *Aims:* To review prevalence and significance of urinary tract (UTI) and genital infections (GI) in diabetes and the effects of sodium glucose cotransporter 2 (SGLT-2) inhibitors on these complications.
Data synthesis: The prevalence of asymptomatic bacteriuria (ASB) is 2–3 times higher in diabetic than in non-diabetic women. The treatment of ASB has no impact on the development of UTIs and/or a decline in renal function. Therefore, there is no indication for screening for and/or treatment of ASB. The incidence of UTI is higher and frequently complicated in diabetic patients, particularly in those with longer duration of disease and of older age. There is no consistent evidence of an association between A1c levels, glycosuria and the risk of ASB and/or UTIs. Diabetes is a known risk factor for *Candida* colonization and *GI*, and a poor glycemic control is associated with a higher risk. While patients treated with SGLT-2 inhibitors may have a non-significant increased risk of UTI, they have a clearly increased risk of GI; most of these infections are mild, easy to treat, and the rate of recurrence is low.
Conclusion: Diabetic patients are at high risk of UTIs and of GI. Only GI are associated with poor glycemic control. Although patients treated with SGLT-2 inhibitors have an increased 3–5 fold risk of GI, proper medical education can reduce this risk.
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Background

Diabetes mellitus and infections

Diabetes mellitus (DM) is a condition predisposing to infections. In the United States, 8–12% of the nearly 6 million diabetics annually hospitalized since 2006 were admitted for infection management and infection was responsible for over $48 billion dollars in hospital charges [1].

Epidemiological data on the association between diabetes and infection point to a complex picture with limited evidence that diabetes is associated with an increased risk of mortality from infections in general [2–5]. However, a number of infectious diseases, such as urinary tract infections (UTI) and mucosal candidiasis are commoner and more severe in persons with diabetes than in the general population. A few specific infections occur almost exclusively in DM: this is the case of invasive otitis externa, rhinocerebral mucormycosis, emphysematous cholecystitis, emphysematous pyelonephritis [2,6–9].

Although several studies have documented an association between the degree of glycemic control and the

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incidence and/or severity of infectious complications [10−14], still the relationship between DM, hyperglycemia, immune function and infections is complex, and many issues remain unresolved [15].

Different antihyperglycemic agents have been analyzed regarding the risk of infection. In particular, the increased risk of upper respiratory tract infections with the use of dipeptidyl peptidase inhibitors [16] has not been confirmed by further studies [17−21].

More recently, the use of sodium glucose cotransporter 2 (SGLT-2) inhibitors has been associated with an increased risk of UTI and genital infections (GI): this issue will be discussed in detail below.

Methods

A systematic literature review was performed using the PubMed databases with the search limited to studies published from January 1990 to December 2015, in English language and including at least 100 patients. Relevant articles were identified by using the key terms diabetes mellitus and infection, urinary tract and genital infection and diabetes, canagliflozin, dapagliflozin, empagliflozin, and SGLT-2 inhibitors.

Urinary tract infections in diabetic patients

Several studies show an association between type of DM and UTI. Diabetic women have a higher incidence of asymptomatic bacteriuria (ASB) and of UTI than non-diabetic women. The evidence regarding ASB in diabetic men is less clear [22,23].

Asymptomatic bacteriuria

The prevalence of ASB has been reported to range between 8 and 26% [22−25] without a clear association between A1c and ABS risk. In an Israeli study [26], the absence of increased risk of ASB in diabetic women was explained by a protective effect of circumcised partners.

In a systematic review and meta-analysis of published data ASB was present in 12.2% of patients with diabetes and in 4.5% of healthy control subjects: ASB risk was three times more common in diabetic patients, with the prevalence higher in both women (14.2 vs 5.1%; odds ratio 2.6) and men (2.3 vs 0.8%; odds ratio 3.7) [27].

No correlation was found between ASB and renal function decline after 6 years follow-up in a cohort of 644 diabetic women [28]. Furthermore, randomized trials on antimicrobial therapy of ASB showed that most treatments were followed by subsequent recolonization, and that treatment does not reduce complications [29−31].

Symptomatic urinary tract infections

In a large retrospective cohort study [7], comparing 513,749 diabetic patients with 513,749 non-diabetic persons, the risk ratio for cystitis in the diabetic group was 1.39 (95%CI 1.36−1.42), and was 1.95 (95%CI 1.78−2.13) for pyelonephritis. In the above-mentioned study [25], the UTI incidence per 100 person-years was 12.2 for diabetic women and 6.7 for non-diabetic women (RR 1.8; 95%CI 1.2−2.7); at multivariate analysis, the increased UTI risk was mainly observed in women taking insulin and with longer diabetes duration. The microorganisms isolated from diabetic women with UTI did no differ from non-diabetic women's isolates. No clear association was found between A1c levels and UTI risk [25].

In a prospective cohort study [8] involving 7417 diabetic patients and 18,911 control patients, the adjusted odds ratio for urinary tract infection was 1.96 (95%CI 1.49−2.58) for patients with type 1 DM and 1.24 (95%CI 1.10−1.39) for patients with type 2 DM.

In 1157 type 2 diabetic patients, the occurrence of UTI was associated with age, duration of diabetes, and poor glycemic control [32].

In an observational study [33] conducted in 135,920 diabetic patients and matched controls, the incidence of UTI was 46.9 per 1000 person-years (95%CI 45.8−48.1) in type 2 diabetic patients and 29.9 (95%CI 28.9−30.8) in patients without diabetes. Compared to non-diabetic patients, the risk of UTI for diabetic patients was 1.53 (95%CI 1.46−1.59).

In a study on the disease burden of UTI among 73,151 type 2 diabetic patients [34], 8.2% had one or more UTI episodes within the year (females 12.9%, males 3.9%); while the risk of UTI in women was higher only in the group older than 75 years; in men, a steady increase in the prevalence of UTI was observed across all age groups.

UTI have a more severe and complicated course in diabetic patients: diabetes increased the probability of acute pyelonephritis requiring hospital admission 5−30 fold [35,36]. Bacteremia has also been found to be 4-fold commoner in diabetic versus non-diabetic patients [37].

Host factors

High A1c levels have not been consistently associated with the occurrence of ASB or UTI. In a population-based cohort study of 2737 type 2 diabetic patients who switched from oral antihyperglycemic drugs to insulin therapy, with or without tightened glycemic control, no evidence was found of a decreased risk of antibiotic-treated UTI episodes following the switch [38].

Glycosuria was not a risk factor for ASB or UTI in a few series [23,39]; the evidence that patients with familial renal glycosuria are not at increased risk of urogenital infections underlines that the glucose presence in the urine "per se" does not increase the risk of infection [40].

Sexual intercourse is a known risk factor for ASB, UTI and recurrent UTI both in non-diabetic [41,42] and diabetic women [39].

Pathogens factors

The increased prevalence of UTI in diabetic women is not the result of difference in bacteria, as the same numbers of