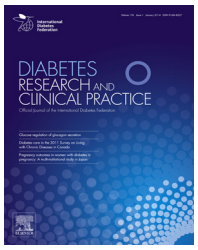
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



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

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ARTICLE INFO

Article history:
Received 19 March 2013
Received in revised form
31 July 2013
Accepted 28 December 2013
Available online 8 January 2014

Keywords:
Type 2 diabetes
Infections
Genital
Urinary
Glucosuria
SGLT2

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.

Contents

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http://dx.doi.org/10.1016/j.diabres.2013.12.052

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