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Antimicrobial resistance in women with urinary tract infection in primary care: No relation with type 2 diabetes mellitus

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ABSTRACT

Aims: To determine if type 2 diabetes mellitus (T2DM) is associated with the spectrum of uropathogens and antimicrobial resistance in urinary tract infections (UTI) in primary care.
Methods: A cross-sectional study in female outpatients ≥30 years with positive urine cultures. T2DM patients were 1:1 matched to controls by age group and general practitioner (GP). GPs were sent questionnaires for additional data. Uropathogens and resistance patterns were compared between patients with and without T2DM. Multivariable regression analysis was performed to assess the independent association between T2DM and resistance to first line treatments, defined as resistance to nitrofurantoin, trimethoprim, fosfomycin, ciprofloxacin, amoxicillin/clavulanic acid and/or trimethoprim/sulfamethoxazole.
Results: In 566 urine cultures, 680 uropathogens were found. Resistance to first line treatment antibiotics was present in 62.5% of patients. Frequencies and resistance rates of uropathogens did not differ between both groups of patients. Previous UTI and previous hospital admission were independent risk factors for resistance, but T2DM was not.
Conclusions: In this study T2DM was not an independent risk factor for antimicrobial resistance in UTI in primary care. Previous UTI and hospitalisation are drivers of resistance and should be included in the decision to perform a urine culture to target first line UTI treatment.

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1. Introduction

Urinary tract infections (UTI) are among the most frequently presented infections in primary care and a large driver of antibiotic prescriptions. Type 2 diabetes mellitus (T2DM) patients have an increased risk for UTI [1–4] and suffer more relapses, recurrences and complications [5–8], probably as a result of a compromised immunity, bladder dysfunction due to autonomic neuropathy, and poor metabolic control [9]. Another hypothesis is that UTI occurs more frequently in T2DM patients due to more resistant uropathogens. Moreover ineffective initial treatment may be a cause of the higher relapse rate. Several studies report that T2DM patients are prone to UTI with extended-spectrum β-lactamase-producing bacteria [10–12], levofloxacin-resistant uropathogens [13] and *Escherichia coli* isolates resistant to second and third generation cephalosporins [14].

Guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases advise more research on the optimal therapy for well-controlled patients with diabetes and do not recommend specific antibiotics for UTI in T2DM patients [15]. Knowledge on pathogens and their resistance patterns in UTI and T2DM could optimize targeted treatment, aiming to reduce relapses, recurrences and complications. This study aims to assess the relation between T2DM and the spectrum of uropathogens and antimicrobial resistance patterns in UTI in primary care.

2. Methods

2.1. Study design and setting

This study was a cross-sectional study in female adult primary care patients for whom a urine culture was performed. Dutch guidelines recommend a urine culture in case of high risk for complicated course, including symptoms of tissue invasion, in case of diabetes if not a first uncomplicated UTI episode, in case of failure of two empiric antibiotic treatments, use of antibiotic prophylaxis for UTI, pregnancy, indwelling urine catheter, impaired immunity, and in case of urinary tract abnormalities [16].

2.2. Study population

All female outpatients ≥30 years old with T2DM and a positive urine culture in the Saltro Diagnostic Center database in 2014 (the leading primary care laboratory in the central region of the Netherlands) were eligible. T2DM was defined by a unique laboratory test code, applied in patients participating in a nationwide primary care diabetes protocol. Urine culture was defined positive in presence of more than 10^4 colony-forming units (CFU) (or 2×10^2 in case of catheter urine). In case of 10^4–10^5 CFU one dominant uropathogen was analysed; in case of $>10^5$ CFU two dominant uropathogens could be analysed. This definition used by Saltro Diagnostic Center is based on international guidelines [17]. Each female with T2DM was 1:1 matched to a non-diabetes patient with a positive urine culture from the same database by sex, age category and general practitioner. Age was categorised as below or at least 55 years to distinguish pre- from post-menopausal females because of assumed differences in etiology and urinary tract complaints. Women with urine cultures including solely yeasts and T2DM patients without a matching non-diabetes patient were excluded. Only the first positive urine culture of each patient in the study period was included in the present analysis.

2.3. Outcomes

The primary outcome was the presence of uropathogens showing resistance to first line treatments, i.e. to nitrofurantoin, trimethoprim, fosfomycin, ciprofloxacin, amoxicillin/clavulanic acid and/or trimethoprim/sulfamethoxazole. Dutch guidelines recommend these for lower (nitrofurantoin, trimethoprim and fosfomycin) and upper UTI (ciprofloxacin, amoxicillin/clavulanic acid and trimethoprim/sulfamethoxazole) [15,16]. Types of uropathogens were the secondary outcome.

Resistance was defined as non-susceptibility to an antibiotic, including resistance and intermediate sensitivity, according to the clinical thresholds of the guidelines of the European Committee on Antimicrobial Susceptibility Testing [17]. Detected uropathogens with 'intrinsic resistance' to one or more of the above-mentioned antibiotics were classified as resistant to that antibiotic(s). Intrinsic resistance is the innate ability of a bacterial species to resist activity of a particular antimicrobial agent through its inherent structural or functional characteristics.

2.4. Laboratory techniques and data collection

Laboratory identification of species and antibiotic susceptibility testing was performed, according to standard laboratory procedures using the Vitek 2 automated system (bioMérieux, France) in all *Enterobacteriaceae*, *Acinetobacter* spp., *Staphylococcus aureus*, *Streptococcus group B* (confirmed with latex agglutination test, Streptex, Remel Thermo Scientific) and *Pseudomonas aeruginosa*. In case of detection of *Streptococcus* spp. other than group B, non-fermentative gram-negative bacteria, *Aerococcus urinae* or when antimicrobial susceptibility testing using the Vitek 2 failed, antimicrobial susceptibility testing was performed using the disk diffusion method (Oxoid, Basingstoke, UK).

Age, the presence of a urinary catheter and the identified uropathogens with their resistance patterns, were extracted from the Saltro Diagnostic Center database. Additionally, standardized questionnaires were sent by postal mail in May 2015 to all study participants' general practitioners (GPs) to complete the dataset. Reminder letters with a copy of the questionnaire were sent to non-responders and finally they were contacted by telephone. The following clinical data were requested: year of diabetes diagnosis, antibiotic use within twelve weeks preceding the UTI, micturition complaints six weeks preceding the UTI, treatment of the UTI before urine culture, treatment switch based on the results of the urine culture, hospitalization and number of UTIs in the previous

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