Diabetes Mellitus and Urinary Tract Infection: Epidemiology, Pathogenesis and Proposed Studies in Animal Models

Swaine L. Chen, Sara L. Jackson and Edward J. Boyko*

From the Department of Molecular Microbiology, Washington University School of Medicine, Saint Louis, Missouri, and Department of Medicine, University of Washington and Seattle Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle (SLJ, EJB), Washington

Purpose: We reviewed the current state of knowledge about urinary tract infection in patients with diabetes from the clinical and basic science perspectives. We identified key knowledge gaps and areas for further research.

Materials and Methods: We performed a focused literature search on certain topics, including clinical studies related to etiology and pathophysiology of urinary tract infection in patients with diabetes, urinary tract infection studies in animal models of diabetes and basic science studies of the molecular mechanisms of urinary tract infection.

Results: Individuals with diabetes are at higher risk for urinary tract infection. Increased susceptibility in patients with diabetes is positively associated with increased duration and severity of diabetes. Clinical epidemiological data identifying mechanisms of increased urinary tract infection susceptibility in patients with diabetes are generally lacking and indicate only that urinary tract infections in women with and without diabetes are qualitatively similar in bacterial etiology and morbid sequelae. Existing animal models for diabetes have not been well characterized for urinary tract infection research. The increased incidence, prevalence and severity of urinary tract infection in patients with diabetes argue for aggressive antibacterial chemotherapy but novel therapies resulting from urinary tract infection research in nondiabetic animal models are still not available.

Conclusions: Future clinical investigations of urinary tract infection in patients with diabetes should focus on how the disease differs from that in patients without diabetes, notably on the role of glycosuria and urinary tract infection risk. Basic science research priorities for urinary tract infection in patients with diabetes should emphasize further development of diabetic animal models for urinary tract infection research and clinical translation of known important virulence determinants into new therapies.

Key Words: urinary tract infections; diabetes complications; diabetes mellitus, experimental; adhesins, Escherichia coli; genomic islands

Abbreviations and Acronyms

ASB = asymptomatic bacteriuria

Hb = hemoglobin

IBC = intracellular bacterial community

QIR = quiescent intracellular reservoir

TLR4 = toll-like receptor 4

UPEC = uropathogenic Escherichia coli

UTI = urinary tract infection

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* Correspondence: Department of Medicine, University of Washington, 1100 Olive Way, Suite 1400, Seattle, Washington 98101 (telephone: 206-277-4618; FAX: 206-764-2563; e-mail: eboyko@u.washington.edu).

DIABETES mellitus is associated with a higher risk of several infections, of which the most common is UTI. Multiple epidemiological studies show a 1.21 to 2.2 increase in the relative risk of UTI in various cohorts in individuals with diabetes compared to those without diabetes.[1–5] Multiple potential mechanisms unique to diabetes may contribute to this increased susceptibility to UTI. Higher glucose concentrations in urine may promote the growth of pathogenic bacteria and act as a culture medium. Decreased immune function, such as impaired migration, intracellular killing, phagocy-

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tosis or chemotaxis in polymorphonuclear leukocytes in patients with diabetes, may weaken host defenses against UTI.[6] Lastly, genitourinary neurological damage due to diabetes may result in dysfunctional bladder voiding and relative urinary retention, resulting in conditions conducive to UTI.[7]

Despite increased susceptibility in patients with diabetes UTI appears to be qualitatively the same disease regardless of diabetic state. The same causative organisms and spectrum of sequelae are seen in the 2 patient populations. Therefore, the extensive literature on the mechanisms of UTI pathogenesis are likely directly applicable to the increased UTI burden in the diabetic population. In terms of diabetes specific mechanisms that increase UTI susceptibility, many animal models of diabetes could be relevant. However, to date little has been done to study the mechanisms of UTI in diabetic animal models.

We highlight recent studies of UTI in patients with diabetes, particularly focusing on questions in need of further study. We reviewed the epidemiological data on potential mechanisms of increased UTI in patients with diabetes. We then considered the development of diabetic animal models for studying UTI. Finally, we discuss results in nondiabetic models of UTI pathogenesis that are relevant to the development of new UTI therapies.

MECHANISMS OF INCREASED UTI SUSCEPTIBILITY

Increased Glucose

Bacteria are expected to grow more readily in urine with a higher glucose level and patients with diabetes are indeed more likely to have ASB.[8] However, a direct relationship between increased serum or urine glucose and an increased risk of UTI has not been clearly demonstrated in any study to our knowledge. Instead the UTI risk correlates with the degree of glycemia, as measured by HbA_{1c}, which also serves as a proxy for glycosuria.

In a case-control study of postmenopausal women, including 781 cases, of whom 0.4% had type 1 and 12.6% had type 2 diabetes, and 849 controls, of whom 0.4% had type 1 and 6.4% had type 2 diabetes, there was no association between HbA_{1c} greater than 8.0 gm/dl and the odds of UTI.[2] Similarly a 2-year prospective study of 1,017 postmenopausal women, including 3 with type 1 and 215 with type 2 diabetes, also showed no dose-response relationship between HbA_{1c} categories and UTI risk.[1] ORs trended upward but were not statistically significant, perhaps due to the large proportion of women in the lowest category (67% with HbA_{1c} less than 7.5 gm/dl).[1] These studies also demonstrated an increased risk of UTI in patients treated with oral medication or insulin. In the prospective study a longer history of diabetes (10 years or more) was associated with an increased UTI risk.[1]

Geerlings et al prospectively assessed 589 women with type 1 or 2 diabetes for incident UTI.[9] HbA_{1c} was again not associated with UTI risk. Finally, a recent study of 528 women taking part in the Epidemiology of Diabetes Interventions and Complications Study Cohort with type 1 diabetes also showed no association between recent HbA_{1c} levels and the prevalence of cystitis in the preceding 12 months.[10] Notably 85% of this population was younger than 50 years and had well controlled type 1 diabetes (mean HbA_{1c} 7.9 gm/dl). Thus, the UTI risk does not correlate with the degree of glycemia (HbA_{1c}) regardless of patient age or diabetes type. UTI risk is associated with increasing duration and severity of diabetes. Because HbA_{1c} as a proxy for urine glucose is not clearly related to UTI risk, additional research is needed to better define the role of glycosuria in the pathogenesis of this infection in individuals with diabetes.

Host Response

Geerlings et al recently reviewed their extensive investigations of ASB, host response and pathogen characteristics in patients with diabetes.[8,11–13] In their large prospective cohort of women with diabetes ASB was not associated with a greater decrease in renal function after 6 years of followup but it was a risk factor for symptomatic cystitis.[9,14] Also, these studies showed differences in host granulocyte function with lower urinary interleukin-6 and 8 in patients with diabetes with ASB compared to those without diabetes with ASB. Furthermore, Escherichia coli expressing type 1 fimbriae showed greater adherence to uroepithelial cells in patients with diabetes, particularly in those with higher HbA_{1c}.[13,15]

Causative Organisms

Boyko et al identified the causative organism in culture confirmed UTIs in a prospective study of postmenopausal women.[1] No relationship between uropathogen prevalence and diabetes status was found. This confirmed the earlier results of the prior case-control study by that group.[1,2] Interestingly prospectively assessed first episodes of ASB were less often caused by E. coli and more often caused by Klebsiella and Enterococcus in women with diabetes than in women without diabetes.[1] This argues that ASB and symptomatic UTI may be different disease processes and bacterial colonization in the absence of symptoms differs in patients with diabetes.

Autonomic Neuropathy and Urinary Retention

Another potential mechanism that could increase the UTI risk in patients with diabetes is autonomic neuropathy involving the genitourinary tract. This re-