

# Urologic Complications of Diabetes

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**D**iabetes and urologic diseases are very common health problems that markedly increase in prevalence and incidence with advancing age (1–3). Diabetes is associated with an earlier onset and increased severity of urologic diseases, resulting in costly and debilitating urologic complications. Urologic complications, including bladder dysfunction, sexual and erectile dysfunction, as well as urinary tract infections (UTIs), have a profound effect on the quality of life of men and women with diabetes. This review presents a comprehensive overview of the current understanding of clinical and basic research on urologic complications of diabetes and recommendations for future directions for research and clinical care.

**BLADDER DYSFUNCTION**—Over 50% of men and women with diabetes have bladder dysfunction (4,5). Current understanding of bladder dysfunction reflects a progressive condition encompassing a broad spectrum of lower urinary tract symptoms including urinary urgency, frequency, nocturia, and incontinence. Previously, the dysfunction has been classically described as diminished

bladder sensation, poor contractility, and increased postvoid residual urine, termed bladder cystopathy (6). However, bladder cystopathy most likely represents end-stage bladder failure with symptoms of infrequent voiding, difficulty initiating voiding, and postvoid fullness and is relatively uncommon.

A number of clinical studies in men and women with diabetes have reported bladder instability or hypersensitivity as the most frequent finding, ranging from 39–61% of subjects (5,7). Diminished bladder contractility or sensation has been found less often (5), and an acontractile bladder appears to be quite uncommon.

## Bladder dysfunction in women

In women, urinary incontinence is estimated to affect nearly 50% of middle aged and older women, leading to significant distress, limitations in daily functioning, and poorer quality of life (8,9). Diabetes has been identified as an important independent risk factor for incontinence in several large observational studies, including the Nurses' Health Study, and is associated with 30–100% increased risk (9–12). This suggests that interventions

that prevent or delay onset of diabetes may also prevent urinary incontinence.

The Diabetes Prevention Program (DPP) randomized trial demonstrated that an intensive lifestyle intervention involving weight loss and exercise reduced the incidence of diabetes among women with impaired glucose tolerance (IGT) (13). Prevalence of weekly stress incontinence was also substantially decreased by the DPP intensive lifestyle intervention. Metformin had no effect on incontinence (14). Weight loss, as has been shown in other studies among women without IGT (15), was the most likely mechanism for the effect of the lifestyle intervention on stress incontinence. Differential diabetes incidence among the treatment groups appeared to play almost no mediating role. Importantly, reducing incontinence may be a powerful motivator for women with IGT to choose lifestyle modification to prevent diabetes. The DPP-Outcomes Study, a follow-up study of the DPP cohort, will examine longer-term effects of the intervention on incontinence.

Obesity is a significant and important risk factor for incontinence and type 2 diabetes. The Action for Health in Diabetes (Look AHEAD) is an ongoing randomized trial examining the effects of interventions designed to produce sustained weight loss on cardiovascular events in 5,145 obese and overweight participants ages 45–75 with type 2 diabetes. An ancillary study will evaluate incontinence annually throughout the trial and postintervention follow-up. The Look AHEAD study offers a unique opportunity to determine whether intentional weight loss also decreases incidence or severity of incontinence and the degree to which this may be mediated by effects on diabetes severity. Additionally, oversampling of racial/ethnic groups at elevated risk of diabetes will help to elucidate differential incontinence patterns observed in earlier studies (11).

Recent large observational studies have identified urge incontinence, an involuntary loss of urine with a feeling of urgency, as increased among women with diabetes, while there was no increased risk for stress incontinence, involuntary

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**Abbreviations:** AGE, advanced glycation end product; ASB, asymptomatic bacteriuria; BPH, benign prostatic hyperplasia; DPP, Diabetes Prevention Program; ED, erectile dysfunction; EDIC, Epidemiology of Diabetes Interventions and Complications Study; ET-1, endothelin-1; IGT, impaired glucose tolerance; IL, interleukin; LUTS, lower urinary tract symptoms; NGF, nerve growth factor; NOS, nitric oxide synthase; PKC, protein kinase C; PMN, polymorphonuclear leukocyte; STZ, streptozotocin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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loss of urine with physical activity (16). Diabetic women treated with insulin are at considerably higher risk of urge incontinence than those treated with oral medications or diet (16). Other aspects of diabetes severity, including glycemic control and microvascular complications resulting in damage to innervation of the bladder, have been suggested as possible mechanisms for increasing incontinence (6). However, most previous studies of incontinence in women with diabetes were conducted in patients attending specialty clinics, did not differentiate between type 1 and type 2 diabetes, and did not adjust for other established incontinence risk factors, including age, parity, and obesity. As a result, little is known about how diabetes may contribute to the incidence or severity of urinary incontinence.

Common treatments for urinary incontinence in women include conservative management (e.g., pelvic muscle training or bladder training), medications, and surgery (17). Because the safety and efficacy of these treatments have not been determined in women with diabetes, conservative management should be the first line of treatment in this population.

### Bladder dysfunction in men

In men, lower urinary tract symptoms (LUTS) are common, age-related complaints that are often attributed to benign prostatic hyperplasia (BPH). LUTS and BPH increase rapidly with age starting at about age 50 years (18). Straining, intermittency, postvoid dribbling, and weak stream may signify urethral obstruction from BPH. However, among men with diabetes, similar symptoms may also result from bladder dysfunction due to denervation and poor detrusor contractility. Other complex associations of LUTS and BPH among diabetic men include symptoms of urgency, frequency, and nocturia that may occur from detrusor overactivity, resulting from BPH, and/or microvascular complications associated with diabetes, increasing hyperactivity of the detrusor. The failure to differentiate LUTS from BPH in studies of diabetic men has contributed to the confusing evidence now seen in the literature (19). Other important factors that contribute to this confusion are concerns such as selected or different study populations, low response rates, inadequate control of potential confounders, and small sample sizes in many studies.

The effect of diabetes on the development or presence of LUTS and BPH remains controversial. As noted, this is due in part to a lack of uniformity in the definition of the outcome. Recent evidence suggests that LUTS may occur more frequently among men with diabetes, with an estimated 25% to nearly twofold increased risk of LUTS in men with diabetes (20–23). Additionally, among men with BPH, diabetes is associated with more LUTS symptoms compared with nondiabetic men (23). BPH may or may not be associated with diabetes. Early studies suggested that diabetes increases prostate size consistent with BPH (24). However, studies using surgery for BPH as the outcome have reported conflicting results, with some reporting that diabetic men were at higher risk (25) and others reporting high blood glucose levels to be associated with a lower risk (26). Two more recent cohort studies found conflicting results. In a study of BPH with LUTS or surgery, a nonsignificant increase was reported (27), whereas a large cohort study using cross-sectional data reported a decreased risk of BPH and increased risk of LUTS (22). In a prospective study of BPH progression, diabetes was found to increase the risk of LUTS but was not associated with an increase in prostate volume (28).

While there is clinical overlap between the presence of BPH and LUTS, they can be manifestations of different pathophysiological pathways mediated through hormonal, environmental, genetic, neuropathic, and (micro)vascular influences, particularly in the diabetic patient. A growing body of experimental evidence indicates that diabetes and obstruction affect different populations of visceral afferents supplying the bladder. In both conditions early alterations in sodium and potassium channels occur similar to neuropathic models. These changes trigger altered excitability, leading to detrusor overactivity and urinary frequency. With time, impaired contractility due to a myopathy can lead to incomplete emptying. Thus, a combination of several factors with differing time courses lead to LUTS and known urodynamic findings, making discerning an etiology and distinguishing classic diabetic cystopathy from neural plasticity accompanying obstruction due to BPH problematic.

Many of the difficulties in reconciling the literature are the broad variation in

definitions used to define BPH and/or LUTS; often they are used interchangeably. Future studies need to take as much care as possible to delineate each condition and to examine each of the underlying pathways before we are able to better understand how diabetes affects BPH and LUTS. Whether outcomes for treatment of LUTS and/or BPH differ between diabetic and nondiabetic men has not been adequately examined in randomized trials.

### Pathophysiology

The biology of diabetes-associated bladder complications can be due to an alteration in the detrusor smooth muscle, neuronal dysfunction, and urothelial dysfunction. The experimental model most often used to assess bladder complications is the streptozotocin (STZ) rat model. Pharmacological studies of smooth muscle dysfunction on isolated diabetic rat bladder strips have generated a considerable amount of controversy. Bladder smooth muscle contraction is mediated by acetylcholine released by the pelvic nerve acting on muscarinic receptors. Responsiveness of diabetic bladder strips to externally applied muscarinic agonists has been reported as increased, decreased, or described as little or no change in responsiveness (29,30). Even when an increased responsiveness is found, the mechanism is unclear. An increase in muscarinic receptor density has been found at both 2 and 8 weeks of STZ-induced diabetes (31). A recent study found an increase in  $\beta_1$ -receptor-mediated relaxation response in isolated detrusor smooth muscle strips from 8- to 10-week STZ-induced diabetic rats (32).

One diabetes-related change that most experts agree on is an increased responsiveness of isolated rat bladder strips to electrical field stimulation (33). Explanations for this change include an increased diabetes-related alteration in membrane lipid composition or increased neurotransmitter release. It has been suggested that changes are related to increased calcium channel activity or enhanced calcium sensitivity (33). Most recently, it has been reported that decreased function was more notable in strips from diabetic rats with enlarged bladders (34). An increased depolarization of myocytes in STZ-induced diabetic rat bladder strips to the application of acetylcholine has been found, indicating en-

hanced muscarinic sensitivity in the diabetic bladder (35).

Neuronal dysfunction may reflect the deficiency of axonal transport of nerve growth factor (NGF) and play an important role in inducing diabetic neuropathy. It has been recently reported in STZ-induced diabetic rats that decreased NGF levels in the bladder and lumbosacral dorsal root ganglia are associated with bladder dysfunction, suggesting the feasibility of NGF gene therapy for the treatment of diabetic cystopathy (36).

The bladder urothelium is important for the regulation of permeability, transport, and endocytosis across the bladder wall. It has become increasingly clear that the urothelium is not only a passive barrier against urea and ion diffusion, but that it can also function as a sensor, controlling bladder function and dysfunction. The effects of diabetes on urothelial receptors and urothelial signaling mechanisms have not been extensively studied. It has been well established that in the STZ-induced diabetic rat model, there are progressive increases in total bladder tissue with hypertrophy of the bladder wall and dilation of the bladder. Both smooth muscle and urothelium (percentage of total tissue) have been shown to increase significantly in a time-dependent manner. Thus, it has been found that the epithelium from STZ-induced diabetic rat bladders was at least twice as thick and heavy than that from controls (37).

**SEXUAL DYSFUNCTION** — Erectile dysfunction, reduced libido, orgasmic dysfunction, and retrograde ejaculation are established complications found with variable prevalence in men with diabetes. Reduced desire, decreased arousal, and painful intercourse are increased sexual problems in women with diabetes, with a reported prevalence of 18–42% (38,39). Whether the same pathophysiological mechanisms are involved in male and female sexual dysfunction and in patients with type 1 and type 2 diabetes has not been determined.

### Male sexual dysfunction

Erectile dysfunction (ED) occurs in a substantial number of men with diabetes, with prevalence estimates ranging from 20 to 71% (2,40,41). ED in diabetic men significantly impacts their quality of life (41,42). The prevalence of disorders of

desire, orgasm, and ejaculation has not been determined.

A number of longitudinal studies have estimated the disease risk of ED in men with diabetes (2,43,44). The 10-year incidence of ED was 25% in a population-based cohort of individuals with type 1 diabetes followed in the Wisconsin Epidemiological Study of Diabetic Retinopathy (43). The Massachusetts Male Aging Study (44) found that the crude incidence of ED in the men with diabetes was 50.7 per 1,000 population-years versus 24.8 in those without diabetes. This figure was similar to results in a convenience sample of 1,010 men with diabetes (68 per 1,000 population-years) (2).

Risk factors associated with an increased risk of ED include hypertension, lipid disorders, coronary heart disease, LUTS, older age, higher BMI, and cigarette smoking. In men with diabetes, the relative risk for ED increases with poor glycemic control, duration of diabetes, and the number of other nonurologic complications of diabetes (i.e., retinopathy, nephropathy, and limb loss) (40,45–47). Studies that focus on the impact of race/ethnicity, modifiable risk factors (e.g., weight loss), and comorbidities on ED are still needed. Recently investigators reported a decrease in relative risk of ED with increased physical activity (48). Whether this reduced risk applies to diabetic men is not known.

Randomized trials demonstrated the success of pharmacological treatment of ED. Phosphodiesterase-5 inhibition leads to significant improvements in function in 50–70% of type 1 and type 2 diabetic patients with ED and controlled hyperglycemia (49,50). However, the efficacy is reduced compared with nondiabetic populations (51). Nonresponders to oral treatment benefit from intracavernosal injections of prostaglandin-E1 and related agents, as >80% of men with diabetes develop adequate penile rigidity (52).

As a result of diabetes, progressive replacement of cavernosal smooth muscle by fibrosis may lead to complete erectile failure (53). Effective surgical interventions in such cases are limited to penile implants. The risk of periprosthetic infection after implantation in diabetic men ranges from 3.2–15% (54). The relationship between glycemic control and risk of infection was not confirmed in a prospective trial (54), although the study may have been underpowered.

The reduced efficacy of all treatments makes diabetic men a population for whom novel prevention and early intervention strategies are needed. Pharmacological approaches targeting smooth muscle cells and neuronal tissue are most relevant (55,56). Examples include administration of vascular endothelial growth factor (57) and immunophilin ligands (58) in animal models of ED. Approaches such as gene therapy that deal with the impaired delivery of nitric oxide (NO) to cavernosal smooth muscle cells may be most important for men with diabetes who develop severe ED (59,60).

**Pathophysiology.** NO from nonadrenergic noncholinergic neurons and the endothelium is required to induce smooth muscle relaxation in the corpus cavernosum, resulting in sinusoidal filling and penile erection (61). When compared with control subjects, diabetic men with ED have impaired neurogenic and endothelium-mediated relaxation of smooth muscle, increased accumulation of advanced glycation end products (AGEs), and altered expression of arginase, a competitor with NO synthase (NOS) for its substrate L-arginine (62,63).

**Human studies.** Neuropathy and arterial disease have all been implicated in the pathogenesis of diabetic ED (64,65). Complications of diabetes that are associated with an increased risk of ED include peripheral or autonomic neuropathy, nephropathy, and retinopathy (2).

Nocturnal penile tumescence testing has been used to infer parasympathetic damage of the penis in diabetic men without vascular disease (65). Neurodiagnostic tests have confirmed that diabetic men with ED have altered conduction of both unmyelinated lower-extremity sensory fibers (66,67) and myelinated pudendal somatosensory fibers. However, diagnostic tests that measure autonomic nerve function and the integrity of cavernosal innervation require development and validation.

Adequate arterial inflow is necessary for erection, and cavernosal arterial morphology, flow (68), and diameter differ between diabetic and nondiabetic populations with ED. Overall, the preponderance of human studies suggests that neuropathy is the most important risk factor associated with ED in diabetes, leading to impaired NO signaling. Whether microangiopathy directly impairs erectile function or merely mediates autonomic neuropathy is unknown.

**Animal studies.** The proposed mechanisms for ED in experimental models of diabetes include central and/or autonomic neuropathy, smooth muscle cellular dysfunction, endothelial dysfunction, and tissue remodeling (69–72).

Downregulation of the neuronal isoform of NOS has been demonstrated in rats with both type 1 and 2 diabetes (73). A recent study suggests that penile nitrergic nerves undergo a selective degenerative process in two phases (74). In the first phase, nNOS protein is depleted in the axons with resultant impairment of erectile function. In the second phase, a synergistic action of endogenous NO and accumulated AGEs in the autonomic ganglia results in selective nitrergic apoptosis. Mechanisms responsible for this neural degeneration and other vascular complications of diabetes may include increased polyol pathway flux, intracellular AGE accumulation, activation of protein kinase C (PKC), and increased flux through the hexosamine pathway (75).

Studies in diabetic animals have identified abnormalities in the central nervous system, spinal cord, autonomic ganglia and nerves, and in the penis. The result of neural degeneration may be to induce apoptosis, cell turnover, and tissue remodeling in the cavernosal spaces. Extensive smooth muscle and endothelial degradation in the corpora cavernosa of diabetic penis has been noted in a model of type 1 diabetes (69). This degradation was accompanied by profound ED, significantly decreased expression of the morphogenic protein sonic hedgehog (Shh) in the smooth muscle of the corpora cavernosa, and increased Shh mRNA expression in the nerves, corpora, and urethra (76). Taken together, these results suggest that in diabetes, ED is the result of a neuro-pathic process leading to denervation of the major pelvic ganglia and cavernous nerves, which in turn results in extensive but truncated tissue remodeling.

Vasoconstrictor signaling pathways are important physiological modulators of the erectile process, and perturbations in these pathways may contribute to the pathophysiology of ED (77). In experimental diabetes, penile smooth muscle has augmented force responses to two important vasoconstrictors, endothelin-1 (ET-1) and the  $\alpha$ -adrenergic agonist phenylephrine (78). Investigators hypothesized that a  $Ca^{2+}$ -sensitization pathway regulates smooth muscle con-

tractile tone, and  $\rho$ -kinase and PKC have been implicated as proteins that promote penile flaccidity (79,80). Diabetic Zucker rats with impaired erections demonstrated increased phenylephrine and ET-1 constrictive activity along with elevated expression of PKC isozymes and RhoA and  $\rho$ -kinase (C. Wingard, unpublished data). Other studies have shown increased sensitivity to ET-1 and increased  $\rho$ -kinase expression using diabetic rabbits (78). The conclusion drawn from these studies is that in diabetes, elements of a  $Ca^{2+}$ -sensitization mechanism participate in impairment of smooth muscle relaxation in the penis.

Delineation of the interaction among PKC, RhoA/ $\rho$ -kinase, and NO/cGMP signaling, the relative contribution of each to neurally generated penile erection, and their potential alterations in diabetes requires further study.

#### Female sexual dysfunction

Female sexual dysfunction is associated with biological, psychological, and social determinants (3). It includes disorders of desire/libido, arousal, inhibited orgasm, and sexual pain (81). Prevalence increases with age, cardiovascular disease, diabetes, cancer, hysterectomy, and neurological conditions (38,82).

Studies of female sexual dysfunction in women with diabetes are limited. Prevalence of dysfunction has been reported in 18–27% of women with type 1 diabetes and in 42% of women with type 2 diabetes (83,84). Women with type 1 diabetes have a nearly twofold greater prevalence of sexual dysfunction than women without diabetes (83). Women with more diabetic complications have more sexual dysfunction. Psychological factors including depression, adaptation to diabetes, and quality of partner relationship are likely to contribute to the sexual dysfunction of women with diabetes and require quantification in future studies. As female sexual complaints may be ignored by caregivers and patients alike, clinicians should be encouraged to query patients about these issues.

In vitro and in vivo approaches may provide insights into disease mechanisms (85–87). Hormonal determinants and possible therapies in women remain controversial (88). The safety and efficacy of testosterone (89) or sildenafil citrate (90) have not been studied in women with diabetes.

#### ASYMPTOMATIC BACTERIURIA AND SYMPTOMATIC UTIS

— Over the years, evidence from many epidemiological studies have suggested that asymptomatic bacteriuria (ASB) and symptomatic UTIs occur more commonly in women with diabetes than in those without diabetes (91). Most of these studies, however, were not prospective cohort designs and are thus subject to multiple biases characteristically associated with case-control, retrospective, or cross-sectional studies. Further, the majority of the data has been collected in patients with type 2 diabetes and in women; therefore, data regarding these relationships in type 1 diabetes and in men are less available. Many of these studies also failed to adjust for relevant confounding variables or comorbidities, and many were done before widespread use of improved methods of glycemic control.

Recent studies have focused on the relationship of ASB to diabetes (92–94). In women without diabetes, ASB is relatively uncommon and increases risk of UTI but does not lead to serious sequelae (95). Diabetic women have a two- to threefold higher prevalence of ASB and are at risk for developing more serious consequences (92,93). For women with diabetes and ASB, those with type 2 diabetes have an increased risk for development of a symptomatic UTI (96), and women with type 1 diabetes are at an increased risk for pyelonephritis and subsequent impairment of renal function (94).

Assuming that ASB is more common and that the consequences of ASB may be deleterious among women with diabetes, the question as to whether to attempt to eradicate ASB in women with diabetes is of considerable relevance. In a randomized controlled trial of type 1 and type 2 diabetic women with ASB, women were randomized to treatment with antimicrobials or no treatment for episodes of ASB >3 years (97). Importantly, the study demonstrated that screening and treatment of episodes of ASB had no impact on overall occurrence of symptomatic UTI or hospitalizations.

Recent studies have demonstrated an increased risk of symptomatic UTIs primarily in women with type 2 diabetes. In postmenopausal women, type 2 diabetes has been associated with a twofold increased risk for UTIs (98–100). Additionally, women on treatment with oral

hypoglycemics or insulin have a three- to fourfold higher risk of UTI, possibly indicating an association with severity of diabetes (98).

Knowledge of risk factors for UTIs in diabetic women is important to identify women in need of therapy to prevent serious complications. Currently, risk factors for UTI in diabetic women are not well defined and may differ by type of diabetes. ASB increases risk for UTI among women with type 2 diabetes (96). However, as previously stated, screening and treatment of ASB have not shown benefit (97). Among women with type 1 diabetes, sexual activity has been identified as the most important risk factor for the development of UTI, similar to women without diabetes (96,101). Continuous or postcoital prophylaxis with low-dose antimicrobial agents as well as intermittent self-treatment with antimicrobials are recommended strategies to prevent recurrent UTIs in women without diabetes (102). However, trials have not been performed in women with diabetes. Although previously suggested as possible risk factors, duration of diabetes or elevated HbA<sub>1c</sub> levels have not been shown to increase the risk of UTI in recent studies (96,98).

Among the most striking effects of diabetes with regard to UTI appears to be the associated risk of infections progressing to complications, severe outcomes, or being due to unusual infecting organisms. For example, emphysematous cystitis and pyelonephritis, relatively rare infections, occur almost exclusively in diabetic patients (91). Other clinical manifestations that are unique or strongly associated with diabetes include abscess formation and renal papillary necrosis. Bacteremia secondary to UTI and pyelonephritis may also be more common in patients with diabetes. Also of importance is the fact that many diabetic patients are infected with non-*Escherichia coli* species, in particular *Klebsiella*, other gram-negative rods, enterococci, and group B streptococci (96,103). Additionally, urinary infections and ASB with *Candida albicans* occur commonly in diabetic women but infrequently in other women (91). Thus, although not documented in prospective studies, there appears to be a clear association of unusual infecting organisms and unusually severe clinical manifestations in patients with both type 1 and type 2 diabetes, primarily women. These obser-

vations should be reevaluated in the light of recent concepts of the pathogenesis of UTI (104).

**Pathogenesis.** Clinical observations have suggested various pathogenic mechanisms of UTI in patients without diabetes, generating extensive laboratory studies of concepts such as the importance of pathogen virulence in the urinary tract. Several recent studies have applied principles of uropathogenesis developed for uncomplicated UTI to understanding the pathogenesis of UTI among patients with diabetes.

The development of UTI in women is preceded by colonization of the vaginal and periurethral epithelium by the infecting organism (105). Ascension to the bladder and/or bacteremia may then ensue. *E. coli* causes the overwhelming majority of UTIs among most groups of patients without diabetes and is also the most common cause of UTI among men or women with diabetes in community-acquired or nosocomial UTI. However, *E. coli* among diabetic women causes a significantly lower proportion of UTIs than among nondiabetic men or women (91).

Bacterial pathogenesis in the urinary tract has been extensively investigated for *E. coli* infections of patients without diabetes (106). Uropathogenic *E. coli* are specialized for success in the urinary tract, elaborating virulence determinants such as adhesins (type 1, P and S fimbriae, and afimbrial adhesin), which bind to specific molecules in the uroepithelium, such as glycosphingolipids and uroplakins (106). Additional virulence factors of *E. coli* associated with UTI and other extraintestinal infections include hemolysin, lipopolysaccharide, cytotoxic necrotizing factor, siderophores, and others (106).

Several older studies of *E. coli* virulence determinants among organisms cultured from patients with diabetes and other medically compromising conditions demonstrated a decreased prevalence of these urovirulence factors (107). However, a recent study examined the prevalence of virulence factors of *E. coli* isolated from episodes of ASB from diabetic women, correlated these with the patients' clinical characteristics, and then compared the results with those of historical control subjects (108). In contrast with the prior finding, the prevalence of virulence factors among the ASB isolates from women with diabetes was nearly identical to findings among ASB isolates

from patients with no medically compromising condition, except for a reduced frequency of specific O:K:H serotypes associated with UTI (108). Three virulence determinants were associated with a decline in renal function (108).

Another recent study examined the ability of three representative clinical isolates of uropathogenic *E. coli* to adhere to uroepithelial cells collected from urine of women with and without diabetes (109). Uropathogenic *E. coli* expressing type 1 fimbriae but no P fimbriae were twice as adherent to cells from women with diabetes as compared with cells collected from the women without diabetes (109). No differences in adherence were seen using the *E. coli* strain expressing no known uropathogenic adhesins or for the isolate expressing only P fimbriae (109). These data suggest that uroepithelial cells from women with diabetes may have intrinsic differences in nature and/or amount and/or affinity of binding receptors for type 1 fimbriae, such as uroplakins.

Because of known alterations in polymorphonuclear leukocyte (PMN) function in high-glucose states, it has been suggested that leukocyte dysfunction occurs in patients with diabetes and increases risk of UTI. However, it has been difficult to correlate in vitro findings with clinical effects. A recent, well-designed study of diabetic women found no differences in five standard measures of PMN function among PMNs isolated from women with diabetes, with or without ASB, as compared with cells isolated from control subjects without diabetes (110). Adaptive immune functions appear to be intact in diabetes, based on findings of normal antibody production and responses to vaccines.

Abnormalities in innate immune functions may also occur in diabetes, but these have not been systematically investigated. Some studies have shown increased baseline levels of cytokines (e.g., interleukin [IL]-6 and IL-8) in serum from patients with diabetes (111). Results of studies of stimulating immune cells from diabetic patients have been conflicting (112). One recent study found that monocytes from women with type 1 diabetes produced lower amounts of proinflammatory cytokines upon stimulation with lipopolysaccharide when compared with cells collected from women without diabetes (113). Women with diabetes who developed bacteriuria also produced

lower urinary IL-6 concentrations, as compared with specimens from bacteriuric control subjects without diabetes (113).

Antimicrobial peptides, an important component of host defense in infections occurring at mucosal surface, such as UTI, have been scarcely investigated in diabetes. There is evidence that AGEs, found in serum of diabetic subjects, may inhibit the function of components of the innate immune system, such as lactoferrin and lysozyme (114). It is not clear what role lactoferrin and/or lysozyme might play in the defense against UTI. On the other hand, human PMNs produce  $\alpha$ -defensins, and  $\beta$ -defensins are synthesized at epithelial surfaces including the upper respiratory tract, nasal mucosa, tongue, kidney, pancreas, colon, female reproductive tract, and conjunctiva (115).  $\beta$ -Defensins have also been detected in urine (116). Additional studies of potential adaptive and innate immune dysfunction in diabetes and its potential effect on the risk of UTI are warranted.

**CONCLUSIONS** — Although urologic complications are common and major health problems in men and women with diabetes, data to define expected prevalence, incidence, and risk factors as well as interventions to reduce the risk of developing these complications are limited. Intensive glycemic control delays the onset and progression of microvascular complications of diabetes in both type 1 and type 2 diabetes (117,118). If microvascular complications also damage the vascular and neurologic innervation of the urethral sphincter, bladder, and corpora cavernosa, then intensive glycemic control may prevent or improve severity of urologic complications.

Data on lower urinary tract symptoms and incontinence, sexual and erectile dysfunction, as well as UTIs, are currently being collected in the Epidemiology of Diabetes Interventions and Complications Study (EDIC), a prospective cohort of participants from the Diabetes Control and Complications Trial (DCCT). The EDIC offers a unique opportunity to further understand the epidemiology of urologic complications among a well-characterized cohort of men and women with type 1 diabetes. Most importantly, analysis of EDIC urologic complications data will determine whether intensive glycemic control during the DCCT that re-

duced the development of retinopathy, nephropathy, and neuropathy in participants of EDIC also reduce the risk of developing urologic complications. Similar studies would be useful among men and women with type 2 diabetes.

Clinical outcomes of common treatments for urologic diseases among diabetic men and women have not been critically examined. Large randomized controlled trials are needed to assess the efficacy and safety of conservative, pharmacologic, and surgical treatments of urologic complications.

Additionally, the pathophysiology and possible mechanisms by which diabetes might promote urologic complications are not clear. The multicellular composition of bladder and erectile tissue make it unlikely that a single mechanism underlies both voiding and sexual dysfunction in diabetes. The complex impact of hyperglycemia on nerve, epithelium (or endothelium), and mesenchymal components of genitourinary organs points toward multiple future therapeutic classes that may be relevant during specific phases of diabetes.

In summary, new research initiatives are needed to further understand the dimensions, including possible basic disease mechanisms, and burden of urologic complications as a health outcome in men and women with diabetes. The paucity of knowledge has been a barrier to developing the best methods of prevention and treatment of urologic complications.

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