SEMINARS IN
NEPHROLOGY

Diabetic Uropathy

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Diabetes mellitus (DM) is becoming more common in the United States affecting an estimated 18.2 million Americans. Not only is the number of American's with DM staggering, but so are the medical and economic costs of DM. DM accounts for nearly 15% of all health care costs in the United States.[1] The chronic hyperglycemia of DM is associated with long-term damage, dysfunction and failure of multiple organ systems, including the genitourinary system. Genitourinary complications are common among diabetics. Of individuals diagnosed with DM, 80% have lower urinary tract complications, while 50% develop nephropathy and 35-75% develop sexual dysfunction. In order to decrease the number and severity of diabetic urologic complications, early recognition and a more comprehensive understanding of how diabetes impacts the genitourinary tract is imperative.
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Diabetes mellitus (DM) is becoming more common in the United States. From 1980 to 2003, the number of Americans with diabetes more than doubled (from 5.8 million to 13.8 million). The Center for Disease Control estimates that 18.2 million Americans, 6.3% of the population, have DM. Of the 18.2 million, 5.2 million are undiagnosed. Not only is the number of Americans with DM staggering, but so are the medical and economic costs of DM. DM accounts for nearly 15% of all health care costs in the United States.[1] The National Institutes of Health-National Institute for Diabetes and Digestive and Kidney Diseases Bladder Research Progress Review Group's August 2002 report noted that "because diabetes significantly alters the urinary tract, a large portion of people who have this disease will develop costly and debilitating urologic complications. . .Unfortunately, the mechanisms involved are poorly understood. The paucity of knowledge has been a barrier to developing the best methods of prevention and treatment of urologic complications."

The chronic hyperglycemia of DM is associated with long-term damage, dysfunction, and failure of multiple organ systems, including the genitourinary system. Genitourinary complications are common among diabetic patients. Of individuals diagnosed with DM, 80% have lower urinary tract complications, 50% develop nephropathy, and 35% to 75% develop sexual dysfunction. In this article the urologic complications of DM are reviewed.

Diabetic Cystopathy

More than 50% of diabetic patients have bladder dysfunction.[2] Classically, diabetic bladder dysfunction had been called *diabetic cystopathy*, a constellation of clinical and urodynamic findings associated with long-term DM. Diabetic cystopathy is characterized by decreased bladder sensation, increased bladder capacity, impaired detrusor contractility, and increased residual urine.[3,4] However, more recent research suggests that diabetic bladder dysfunction is a progressive condition with a spectrum of clinical findings and symptoms.

Some studies support the classic findings of diabetic cystopathy whereas others do not. Ueda et al[5] and Frimodt-Moller et al[6] consistently found increased bladder volume at first sensation to void and a decrease in detrusor contractility, resulting in increased residual urine, in diabetic patients. In contrast, a number of clinical studies have reported bladder instability as the most common finding among diabetic patients. In a study of 182 diabetic patients, Kaplan et al[3] found 55% to have detrusor instability whereas only 23% had impaired contractility. A study by Starer and Libow[7] elderly diabetic patients showed similar results with 76% of diabetic

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patients showing involuntary bladder contractions. These studies suggest that diabetes causes different types of bladder dysfunction with diabetic cystopathy being only one of the conditions found along the spectrum of diabetic bladder dysfunction. Therefore, the International Continence Society recommended the term *diabetic bladder dysfunction* to describe the problems of storage, voiding, or both that occur in diabetic patients.[8]

Diabetic bladder dysfunction has been attributed to several causes including autonomic axonopathy, diuresis-induced myopathy, metabolic alterations in adrenergic and cholinergic receptors in detrusor smooth muscle, and oxidative stress leading to smooth muscle damage and apoptosis.[9]

Diabetic bladder dysfunction can lead to secondary complications including recurrent or atypical urinary tract infections that are assumed to originate from increased postvoid residuals. Other complications include pyelonephritis, nephrolithiasis, urinary retention, hydrourteronephrosis, and urosepsis.

Diabetic Nephropathy

Diabetic nephropathy is the most common single cause of renal insufficiency in the United States, Japan, and Europe[10] and has been defined classically by proteinuria of more than 0.5 g/24 hours.[11] Between 1994 and 1999, 43.7% of US patients receiving treatment for end-stage renal disease (ESRD) had renal failure as a result of diabetic nephropathy.[1] In 2000, the Medicare and non-Medicare expenditures for the treatment of renal failure totaled $19.35 billion; half of which was used for the treatment of patients with diabetes.[12] ESRD is a significant cause of morbidity and mortality among diabetic patients. Diabetic patients on dialysis have significantly lower survival rates compared with patients with ESRD from hypertension, glomerulonephritis, and other causes.[1]

Diabetic nephropathy is more prevalent among African Americans, Mexican Americans, Native Americans, and Asians than Caucasians.[11,12] Epidemiologic and familial studies of patients with both type I and II DM have shown a genetic susceptibility to the development of diabetic nephropathy.[12,13]

Diabetic nephropathy causes unique structural changes of the glomeruli, tubules, extraglomerular blood vessels, and the interstitium.[1,10,11] The earliest histologic change is thickening of the glomerular basement membrane.[1] This occurs early in the disease, 1 year after the onset of diabetes, and is cumulative.[10] As the disease progresses, there is expansion of the mesangial area.[1] This is caused by an accumulation of extracellular matrix deposition and mesangial cell hypertrophy.[10] Several studies have shown an inverse relationship between the glomerular filtration rate and mesangial expansion.[1,10] Tubular and interstitial changes follow as a result of deteriorating glomerular function.[1]

Despite its frequency and importance, the pathophysiology underlying diabetic nephropathy is incompletely understood. On a molecular level, at least 5 pathways have been implicated in histologic changes induced by DM. Chronic hyperglycemia results in increased polyol pathway flux, increased hexoamine pathway flux, activation of the cytokine transcription factor nuclear factor κ B, increased advanced glycation end-product formation, stimulation of angiotensin II synthesis, and activation of the protein kinase C pathway.[10] All of these pathways cause an overproduction of reactive oxygen species.[10]

The clinical and histopathologic changes associated with type I diabetic nephropathy are classified into 5 stages.[1] These changes are present in variable degrees in patients with type 2 diabetes.[1] Stage I is characterized by an increase in glomerular filtration rate and renal hypertrophy. In stage II there is an increase in glomerular basement membrane thickness and mesangial matrix volume expansion.[1] Stage III is characterized by microalbuminuria and an increase in blood pressure. Stage IV is overt diabetic nephropathy. Stage V is ESRD, characterized by minimal residual renal function requiring either dialysis or renal transplantation.[1]

Diabetic nephropathy, although present in 50% of diabetic patients, does not occur in all diabetic patients. Therefore, the identification of modifiable risk factors is important in preventing disease progression. These modifiable risk factors include hypertension, poor glycemic control, smoking, dyslipidemia, dietary factors, and proteinuria levels.[11]

Sexual Dysfunction

The incidence of erectile dysfunction (ED) among diabetic men ranges from 27% to 75%, depending on the patient's age and duration of diabetes.[14] In a cohort study of more than 31,000 men aged 53 to 90 years, the age-adjusted relative risk for ED among diabetic men compared with men without diabetes was 1.32.[2,14] Among diabetic men the relative risk for ED increases with poor glycemic control, duration of diabetes, and the number of nonurologic complications such as nephropathy and retinopathy.[15]

Risk factors associated with an increased risk for ED include hypertension, dyslipidemia, coronary artery disease, smoking, older age, higher body mass index, and lower urinary tract symptoms (LUTS).[2,4,14]

The etiology of diabetic ED is multifactorial. Neuropathic, vascular, psychogenic, and pharmacologic factors all play a role in ED among diabetic patients.

Erections occur as a result of cavernosal smooth muscle relaxation with resultant increased blood flow into the sinusoids. Nitric oxide released from nonadrenergic noncholinergic nerves and endothelial cells is required to induce cavernosal smooth muscle relaxation. In diabetic men, neurogenic and endothelial-mediated smooth muscle relaxation is impaired secondary to abnormal levels of nitric oxide synthase, nitric oxide, cyclic guanosine monophosphate, and protein kinases.[1] Several animal studies have shown diminished nitric oxide and nitric oxide synthase in cells grown in high-glucose milieus.[1]

Treatment options for diabetic men with ED are similar to those for nondiabetic men. Vacuum-constriction devices offer a noninvasive option effective in 70% of patients with DM.[16] Complications such as petechiae, ecchymoses, and

hematomas can be seen if the device is used for more than 30 minutes.[4] Along with control of hyperglycemia, oral agents are the first line of therapy for ED in patients with DM. Oral agents such as Viagra (Pfizer, Inc., New York) have been shown to be efficacious in diabetic patients. The first study to look at the effect of Viagra in diabetic patients found 50% and 52% of diabetic patients treated with 25 and 50 mg, respectively, had improvement in erections.[17] In a subsequent multicenter, randomized, double-blind, placebo-controlled study, 56% of patients taking sildenafil reported improved erection.[18] The efficacy of sildenafil was not affected by patient age, the duration of ED, or the duration of DM.[18] The newer phosphodiesterase 5 inhibitors, vardenafil and tadalafil, have shown equal efficacy in diabetic patients.[19,20]

Intraurethral suppositories and intracavernous injections also have been proven to be effective in diabetic patients.[1,21-23] The rate-limiting factor for both therapies are side effects. Intraurethral suppositories are associated with penile pain and urethral bleeding, whereas injection therapy has been associated with painful penile sensation, fibrotic changes in the corporeal body, and priapism.

Surgical therapy including penile implants and revascularization typically are reserved for patients who fail all previous modes of therapy.

Similar to male sexual dysfunction, female sexual dysfunction (FSD) is highly prevalent among female diabetic patients. Eighteen percent to 27% of women with type I and 42% of women with type II diabetes report FSD.[15] Female diabetic patients have a 2-fold greater prevalence of FSD compared with nondiabetic women.[15] Yet unlike diabetic male sexual dysfunction, little is known about the pathophysiology or treatment of FSD in diabetic patients. Recent animal studies have shown that similar to male ED, diabetic women with FSD had impaired relaxant responses of vaginal smooth muscle to nitric oxide.[24]

Urinary Incontinence in Women

Several reports indicated that women with either type I or II DM have a higher prevalence of lower urinary tract complications, including urinary incontinence. In several large observational studies, DM was identified as an independent risk factor for urinary incontinence. In 2,763 postmenopausal women the prevalence of stress, urge, and mixed urinary incontinence was significantly higher in diabetic women compared with nondiabetic women.[25]

In a recent cross-sectional analysis of a population-based study of 1,017 postmenopausal women aged 55 to 75 years, 60% of all women reported incontinence in the past month, with 8% having severe incontinence.[26] Women with diabetes reported disproportionately more severe incontinence, difficulty controlling urination, mixed incontinence, use of pads, inability to empty the bladder completely, being unaware of leakage, and discomfort with urination ($P = .06$).[26] Diabetes duration, treatment type, peripheral neuropathy, and retinopathy were associated significantly with severe incontinence in a multiple regression model adjusting for age, education, and history of urinary tract infection ($P = .01$-$.06$).[26]

Several recent large-scale studies showed that diabetes was associated with a 30% to 80% increased risk for urinary incontinence,[27-29] with the risk for urge incontinence (storage problem) increased by 40% to 80% in a multivariate analysis that controlled for stroke and other chronic medical conditions.[28-29]

Conclusions

Diabetes mellitus is a growing health problem worldwide. With more than 18 million people affected, the cost to the health care system and patients quality of life is overwhelming. Urologic complications such as bladder dysfunction, nephropathy, and sexual dysfunction are common among diabetic patients, both male and female. To decrease the number and severity of diabetic urologic complications, early recognition and a more comprehensive understanding of how diabetes impacts the genitourinary tract is imperative.

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