Urologic Complications in Patients with Diabetes

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Ivan Mauricio Schroeder-Ugalde,
Karen Yhadira Sanchez-Lastra, and Angel Enrique Garcia-Cortes

Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases associated with high glucose levels that cause systemic long-term damage, dysfunction, and failure of several tissues [1]. Among the consequences of this chronic hyperglycemic state, patients with DM suffer several urologic complications that involve endothelial and neural damage all along the genitourinary tract with significant economical and quality-of-life costs.

The worldwide incidence of urologic complications associated with DM is increasing because of the high incidence of obesity in the entire world [2]. The effect of obesity in our society is growing at a worrying rate, and it is associated with an increasing risk of noninsulin-dependent diabetes. Clinicians have the opportunity to prevent, diagnose, and change the evolution of these urologic complications among patients with diabetes by maintaining a proper weight [3].

Diabetes has been associated with an earlier presentation and increased severity of urologic complications [4]. DM leads to nerve function disturbance, loss of innervation of neuromuscular nerve terminals, abnormal immune response, and altered sympathetic/parasympathetic innervation [5]. Therefore, peripheral accumulations of fat in the abdominal region of patients with diabetes has been associated to an increased risk of urologic complications such as urinary incontinence, erectile dysfunction, benign prostatic hyperplasia, urinary tract infections, and possibly with cancer [3].

I. M. Schroeder-Ugalde (✉)
Hospital Angeles Universidad and UROMED,
Ciudad de México, CDMX, Mexico

K. Y. Sanchez-Lastra · A. E. Garcia-Cortes
Hospital Regional Lic. Adolfo Lopez Mateos ISSSTE,
Mexico City, Mexico

Bladder Dysfunction (BD) and Cystopathy

Generally, the beginning of bladder lesions of diabetes is not very evident, and they are not recognized until the disease is in the most advanced stages. Between 20 and 50% of all diabetic patients are affected, although some studies raise this figure to 88% of cases. No correlation has been observed between the type and duration of diabetes or the age of the patients, although it was shown that 80% of cases with a neurogenic diabetic bladder have lesions in other organs (kidney, eye, penis, arteries, etc.). (Campbell-Walsh 12 ed).

Bladder dysfunction or dysfunction in the bladder outflow tract attributed to any alteration of the nervous system. Some bladder symptoms that occur in patients with diabetes mellitus are known as diabetic bladder dysfunction or diabetic cystopathy, which include lower urinary tract symptoms (LUTS) characterized by increased postvoid residual volume due to inadequate emptying of the bladder, resulting in increased bladder capacity, worsened by reduced sensation and contraction of the bladder [6].

The cornerstone for evaluation is the questioning of urologic history, sexuality, bowel behavior, and neurologic history. Within the specific urological history, we must take into account the onset of symptoms, relief after urination, the beginning and end of urination, if there is presence of interruption of urination, mode and type of urination, enuresis and a strict record is essential in a urination diary.

Almost half of patients with DM suffer from different degrees of bladder dysfunction (74% men and 59.26% women), which causes an increase in postvoid residual urine and urinary incontinence, causing infections, bladder stones, or eventually kidney damage [7]. In men, bladder disorders are made worse by the enlargement of the prostate associated with age.

In Mexico, approximately 12% of the population suffers from type 2 diabetes mellitus, so the prevalence of bladder dysfunction due to this cause is common in the urological delivery, it is important to know how to detect it and refer it in time to the urology specialist to its timely treatment.

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Obese and diabetic women are expected to have more pelvic floor disorders, such as stress urinary incontinence and overactive bladder [4] that could be related to increased abdominal pressure from the abdominal panniculus that exerts pressure unwanted over the pelvic organs, uterus, bladder, urethral sphincters and vagina [3], peripheral neuropathy, and loss of bladder support. Insulin treatment in women with diabetes mellitus increases the risk of urge incontinence, compared to women treated with metformin, which has no effect on incontinence [8, 9].

Bladder hypersensitivity is reported as the most common finding, ranging from 39% to 61% in patients with diabetes mellitus, in numerous clinical studies [6]. Furthermore, an important predictor of bladder dysfunction is the presence of peripheral neuropathy, renal disease, and the association of metabolic syndrome [4].

Pathophysiology

During the early stages of diabetic cystopathy, there is an increase in the storage capacity of the bladder, which affects its compliance or ability to adapt to pressure as the bladder fills [10]. Several mechanisms have been described that induce abnormalities in bladder function at the detrusor muscle level, including changes in intracellular connections and excitability, muscarinic receptor density, genetic traits, and changes in intracellular signaling. All of these contributing factors result in decreased contractility and increased postvoid residual volume. Compensatory bladder hypertrophy results in increased bladder instability that decreases its contraction force due to collagen deposits, rendering detrusor muscle tension ineffective [10]. Another theory is the associated increase in diuresis due to the hyperglycemic state resulting in neural and endothelial damage, which collectively can lead to detrusor muscle hypertrophy in an attempt to adapt to these changes. On the other hand, abnormalities in calcium and potassium cell wall channels increase detrusor muscle activity and increase hyperactivity [11]. Furthermore, rabbit models have shown that overexpression of aldose reductase and increased lipid peroxidation products result in decreased detrusor contractility [12].

Another problem that influences bladder hypertrophy could be an increase in oxidative stress, associated with greater damage to the bladder muscles [13] or induced by a deficiency in axonal transport of neural growth factor (NGF). Bladder tissue remodeling is also associated with downregulation of tissue growth factor (TGF) and collagen mRNA levels, which induce an increase in elastin synthesis. These factors can result in an increase in bladder compliance in patients with diabetes associated with a reduction in collagen synthesis [14].

Neuronal control of bladder function consists of an interaction between autonomic sympathetic and parasympathetic, somatic afferent and efferent pathways. Patients with diabetic cystopathy have somatic and autonomic neuropathy. In addition, cells subjected to long periods of exposure to hyperglycemia suffer an accumulation of oxidative stress products, which cause axonal degeneration and nerve damage, decrease nerve conduction, trigger diabetic cystophaty, and erectile dysfunction [15]. In addition, decreased bladder filling sensation, caused by nerve damage, can cause excessive distention and increased hypocontractility of the bladder wall in diabetic patients. Diabetic cystopathy also involves neuropathic changes, produced by hyperexcitability of the urethral afferent reflex, leading to external urethral sphincter dysfunction and reduced urethral smooth muscle relaxation with obstruction to urine outflow.

Long-standing diabetes also affects the peristaltic function of the ureters by interfering with ureteral muscle cells and nerve function, causing upper urinary tract dysfunction, urine stasis, and eventually kidney stone formation [5]. The voiding reflex is a neural stimulus controlled by the M2 and M3 receptors. Patients with diabetes have a greater number of muscarinic receptors in the urothelium that increase sensory nerve activity and modify detrusor contraction, causing greater bladder dysfunction and urinary stasis [11].

Clinical Manifestations

In the early stages of the diabetic bladder, compensatory changes maintain the ability to maintain a normal diuresis. In later stages, decreased voiding pressure and increased urethral obstruction lead to larger volumes of postvoid residual urine, producing a wide variety of symptoms ranging from urgency to urinate and incontinence (a sensation urinary leakage) (40% to 80% risk) to the most severe expression of overflow incontinence (in which the bladder empties due to excess residual urine without patient control) [16].

Diabetic patients can complain of lower urinary tract symptoms, including urgency, difficulty in initiating, maintaining and ending urination, inadequate voiding or sensation of residual urine, frequent urination during the day and night, slow or decreased urinary flow of different severity levels. Consequently, voiding reflexes appear to be diminished or inactive, causing a progressive asymptomatic increase in bladder capacity, which can eventually cause urinary retention, bladder stone formation, diverticula, infection, upper urinary tract dilation, and kidney damage. . In contrast, diabetic bladder dysfunction can also present as overactive bladder syndrome with corresponding frequent day and night bladder emptying, urgency, and lower urinary tract symptoms. Hypersensitivity and hypercontractility of the bladder are more common than hypocontractility [6].

Diabetic cystopathy and bladder dysfunction are common in long-standing diabetic patients. They can be asymptomatic or manifest a wide spectrum of clinical symptoms, ranging from voiding discomfort due to overactive bladder and urge incontinence due to decreased bladder sensation, to overflow incontinence and acute urinary retention [4]. Bladder symptoms can be divided into irritating and obstructive. Irritant symptoms involve the overexcited detrusor muscle, causing urgency, polyakiuria, nocturia, and urge incontinence, known as overactive bladder syndrome. Obstructive symptoms include decreased size and strength of voiding flow, terminal dribbling, decreased sensation of a full bladder, and high postvoid residual urine. Obstructive symptoms are related to a pseudo-obstructive bladder, represent the last phase of visceral diabetic neuropathy, and are associated with a low urine flow that can be demonstrated with uroflowmetry, high postvoid residual and urodynamic studies, which show a hypotonic bladder in cystometry caused by a myogenic alteration of the microvasculature and neuronal cells. [10, 17].

Diagnosis

The approach to the study of diabetic cystopathy depends on the individual patients symptoms, severity, renal function, and impact on quality of life. In patients with symptoms of bladder dysfunction, physicians should take a detailed history including the International Male Prostate Symptom Score, physical examination with neurological reflex and rectal examination, presence of pelvic organ prolapse, followed by tests of laboratory to evaluate kidney function (serum creatinine), infections (urine test), and clinical chemistry. Similarly, a sexual history, the presence of genital or sexual dysfunction, the sensation in the genital area, specific to the man (erection, orgasm and ejaculation) and specific to the woman (dyspareunia and orgasm), within the habits bowel movements, presence of fecal incontinence, urgency, rectal sensation, stool pattern, and the onset of this complication. In the neurological history, if you have a congenital or acquired condition, mental status, neurological symptoms, spasticity, or autonomic dysreflexia.

The diagnosis of diabetic neurogenic bladder is based on the performance of a complete urodynamic study (flowmetry, cystometry, electromgraphy, and urethral pressure profiles). The most common findings of the final stages of the disease are the loss of voiding sensation with significant increase of bladder capacity and decreased detrusor contraction (areflexia) with low voiding flow and presence of residual postvoiding urine. The picture must be differentiated from infravesical urinary obstruction, which is achieved with a pressure/flow study. Urodynamic evaluation is an essential component of the examination, although it is not indicated in all cases. It includes cystometrogram, simultaneous flow and pressure studies, sphincter electromyography, and postvoid residue measurement [6]. It is recommended that the patient has to carry out a voiding diary prior to the urodynamic study. Diabetic women have significantly higher nocturia scores on lower urinary tract symptom questionnaires, with weaker urinary flows, reduced voiding volumes, increased residual urine volumes, and lower peak flow rates by uroflowmetry [4].

Treatment

The first step in managing any type of diabetes complications is blood glucose control. The treatment of diabetic cystopathy depends on the severity of the symptoms, but in the early stages, it is basically conservative and, in case of complications, they should be treated accordingly [18]. The treatment of diabetic neurogenic bladder resides in the treatment of symptoms, the prevention of urinary infection, the maintenance of renal function, and continence with an adequate bladder emptying. However, there is no cure for the disease. When there is an unstable bladder, the use of anticholinergics is of great help to improve symptoms (Campbell-Walsh 12 ed). In patients who complain of urgency, different types of first-line therapy are available to control detrusor overactivity, including oral muscarinic drugs, and more uroselective anticholinergics with fewer adverse effects (oxybutynin, tolterodine, darifenacin, or solifenacin). A recently approved β3 adrenergic agonist (mirabegron) that increases urine storage capacity, by direct relaxation of detrusor smooth muscle, can be used to provide rapid relief of symptoms [19, 20]. Infiltration of the detrusor muscle with botulinum toxin has been shown to decrease urge incontinence. A surgical approach could be offered in severe cases of unresolved urge incontinence with selective muscarinic anticholinergics, including bladder denervation, myomectomy, and bladder augmentation with ileal cystoplasty. All of them are associated with the risk of increased postvoid volume, urinary tract infection, kidney damage, and stone formation [18].

In men with additional bladder outlet obstruction associated with an enlarged prostate, initial treatment includes the use of alpha blockers such as terazosin, tamsulosin, and alfuzosin. In advanced stages, transurethral resection of the prostate could be considered.

In cases of failure to empty the bladder, frequent clean intermittent catheterization is the best option to avoid permanent use of indwelling catheters, due to the risk of increased infection rate, lower urinary tract lithiasis, and squamous cell carcinoma of the bladder [21].

All these measures are always carried out to protect kidney function, since, by increasing bladder pressure, due to the increase in urinary volume and the lack of accommodation of the bladder, they can cause a deterioration in kidney

function and worsen the damage per se. That is what diabetes mellitus does to the kidneys (Campbell-Walsh 12ed.). Similarly, within the objectives of treatment, they are to avoid urinary tract infection, achieve or maintain urinary continence, preserve the ability to urinate, and improve the quality of life of the patient.

Benign Prostatic Hyperplasia (BPH) and Urethral Obstruction

Benign prostatic hyperplasia (BPH) is an age-related phenomenon that affects up to 50% of men aged 60–69 years and almost 90% at age 90 [22]. DM is frequently associated with BPH due to the same age of incidence [23]. BPH has been largely associated to metabolic disorders including diabetes, metabolic syndrome, obesity, and hypertension. Preclinical and clinical studies have shown that increased plasma insulin levels are positive independent predictors of BPH, as well as high fasting glucose level and hyperlipidemia; all of them have shown a positive correlation to the progression of BPH [24–26].

Pathophysiology

Several theories have been proposed in the pathogenesis of BPH. The most convincing however is that prolonged chronic ischemia and repeated ischemia-reperfusion injury in the bladder could generate oxidative stress, which increases sympathetic nerve activity and vascular damage, further hypoxia of the bladder and prostate, abnormal cell proliferation, in addition to an increase of lower urinary tract symptoms [22]. Endothelial dysfunction and nitric oxide (NO) deficiency are among the most important factors in the development of diabetic complications, affecting the lower urinary tract as well. Relaxation of the urethral sphincter is partially affected by NO, which in turn causes outflow obstruction and hyper-excitability of afferent neurons associated with progression of diabetes [27]. All these factors, in addition to the increased risk of overactive bladder in diabetic patients are closely related to peripheral nerve irritation [28]. Another possible explanation for the presence of BPH in diabetic patients involves insulin-like growth factor (IGF). Beta cells of patients with Type 2 diabetes secrete higher concentrations of insulin; the resulting hyperinsulinemia stimulates IGF synthesis. Activation of the prostate IGF receptors may also cause prostate growth [29, 30] which could be explained because of homology of insulin and IGF receptors [31] and cross-activity to insulin action [32].

The pathogenesis of BPH is multi-factorial and characterized by basal cell hypertrophy, secretory alterations of luminal cells, infiltration of lymphocytes with production of pro-inflammatory cytokines, stromal proliferation, diminished apoptosis, trans-differentiation and extracellular matrix production, abnormal autonomous innervation, and modification of the neuroendocrine cell function among others [22]. Disturbances in fatty acid metabolism are also influential in the progression of BPH, including inflammation, oxidative stress, peroxidation of lipids and accumulation of 8-hydroxy-2′-deoxyguanosine, and increased androgen synthesis [33].

Clinical Manifestations

Initially, patients with BPH complain of symptoms of LUTS (which already mentioned includes nocturia, frequency, urgency, weakened stream, hesitancy, intermittency, straining, and a sense of incomplete emptying) [34]. Progressive evolution toward complications in the urinary tract is more important than symptoms related to micturition. They are significant and include bleeding, lithiasis, renal insufficiency, and infections [35], but the most serious and painful manifestation is acute urinary retention, the inability to urinate, characterized by intense pain in the pelvis [36].

Diagnosis

Evaluation of BPH in diabetic patients includes a detailed medical history, including LUTS questions, severity, and influence in their quality of life. The American Urological Association Symptoms Index (AUA-SI) is a questionnaire that allows physicians to quantify symptoms at diagnosis and over time in response to treatment. Digital rectal examination should be included in the physical examination. PSA (Prostate-specific antigen), urinalysis, and frequency/volume chart may be filled, as well as uroflowmetry, post void residual ultrasound, and renal ultrasound in order to diagnose complications [34].

Treatment

To avoid complications, effective and conservative drug treatment for BPH is currently available. Patients with a small prostate are routinely treated with alpha-1 blocker monotherapy as first-line therapy, either with nonselective blockers such as doxazosin and terazosin or uroselective blockers such as tamsulosin, alfuzosin, and silodosin. All of them have similar effectiveness but diverse side-effect profiles. Characteristic side effects include postural hypoten-

sion, dizziness, rhinitis, asthenia, sexual dysfunction, and abnormal ejaculation. Storage and voiding symptoms improve briefly after initiation of treatment. Alpha-1 blockers do not prevent BPH progression. For that reason, prostate volume and symptom progression should be monitored during the follow-up of the patient [34, 37].

Patients with a small prostate associated to voiding symptoms, the diagnosis of overactive bladder should be considered and treated as previously mentioned with anticholinergics, keeping in mind the need to monitor by dynamic bladder ultrasound the possibility of urinary retention, even though the risk is low.

In patients with enlarged prostate (over 30–40gr), the use alpha-1 blockers in combination with an alpha 5 reductase inhibitor (finasteride or dutasteride) that block the conversion of dehidrotestosterone from testosterone is highly recommended, in order to diminishing the prostate volume at long term with a faster effect on the relaxation of the bladder neck. In case of failure with all these therapies, the surgical approach is the next option. Transurethral resection of the prostate is the gold standard, but newer techniques such as bipolar resection, and the use of laser vaporization, botox infiltration, cryotherapy and high intensity focused ultrasound among others, represent less invasive approaches than open adenomectomy [36, 37].

Sexual Dysfunction

Men and women with diabetes are affected by sexual dysfunctions, which are defined as the inability to achieve or maintain an adequate sexual response to complete a sexual encounter or intercourse resulting in a satisfactory orgasmic sensation. Sexual dysfunctions include disorders of libido, ejaculatory problems, orgasmic abnormalities, and erectile dysfunction. The reported prevalence of sexual dysfunction in men with type 2 diabetes is up to 46%. Sexual dysfunction in women is harder to diagnose but it has been proposed that its prevalence in type 1 diabetes is 71% and 42% in females with type 2 diabetes [38, 39].

Almost half of nonsexually active men and women with type 2 diabetes report that their sexual life do not fulfills their sexual needs, suggesting that they are more concerned and even more distressed than sexually active patients. Commonly, women argue that lack of sexual activity is related to a number of reasons, including lack of interest, physical problems that make it difficult or unpleasant, absence of partner, or having a partner with physical limitations [40].

Sexual dysfunctions involve a group of alterations that affect significantly the quality of life of these patients and include reduced desire, decreased arousal, orgasmic abnormalities, and painful intercourse [41].

Leading risk factors that further affect diabetic men and women include age, length of diabetes [40] co-medications, obstetric history, neurogenic and vascular complications, and infections among others.

Erectile Dysfunction (ED)

It is defined as a long term, consistent, or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction. It is the third most frequent complication of diabetes and considered as one of the most significant complaints affecting quality of life [42]. Manifestations usually appear after 10 to 12 years after the onset of diabetes, because of diabetic endothelial and neural damage associated with persistent high serum glucose levels [43].

The WHO Global Report on Diabetes states that the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 and that the global prevalence among adults has risen from 4.7% to 8.5% over the same period. The overall prevalence of erectile dysfunction in diabetes is 59.1%, but significantly different across countries, South America 74.6%, Oceania and Africa 71.3%, and lowest amongst North American studies with 34.5% . Diabetic male patients generally have a greater prevalence and an earlier onset of erectile dysfunction than men without diabetes and it appears 10–15 years earlier in diabetic than in nondiabetic men. Erectile dysfunction in diabetics is directly associated with poor glycemic control as well as greater duration and severity of diabetes [44]. Moreover, it has been demonstrated that ED is an early sign of cardiovascular events, particularly coronary heart disease. Prevention of cardiovascular disease through screening and management of cardiovascular risk factors in men with ED is very important [45].

Pathophysiology

The aetiology of ED in diabetes is considered to be multifactorial, pathophysiologic changes associated with diabetes can broadly be classified as vasculopathy, neuropathy, hypogonadism, and local pathological factors.

Men with erectile dysfunction that have macrovascular disease have diminished vasodilating responses causing less relaxation of the vascular smooth muscle tissue because of changes in the vessel that predispose to subsequent atherosclerosis, plaque formation, thrombosis leading to occlusive macrovascular disease, and microvascular disease due to deficient production of nitrate oxide in nonadrenergic noncholinergic neurons and in the endothelium [46]. These

abnormalities are associated with important accumulation of advanced glycation products, altered expression of arginase, a competitor of the NO synthase for its substrate L-arginine [47, 48]. All of these abnormalities cause a tendency toward vasoconstriction, such as that caused by phenilephrine and endothelin-1, resulting in lack of vasodilatation and inadequate penile erection.

Numerous mechanisms play important roles in the pathophysiology of erectile dysfunction in diabetic males, one of them is the polyol pathway, which forms sorbitol by action of the enzyme aldose reductase. Sorbitol accumulates inside the cells, causing diminished myo-inositol levels (a precursor of the phosphatidylinositol), required for the adequate functioning of the Na-K ATPase pump. Increased sorbitol concentrations additionally produce progressive peripheral nerve damage [49].

Regarding vascular component, endothelial damage is a central issue in ED, because in comparison with healthy males, diabetic male patients have a diminished arterial inflow, which has been observed microscopically with reduced diameter and deficient morphology of the vascular wall [50]. Contraction of cavernosal smooth muscle cells is also affected by hyperglycemia, which results in an increased forced response to vasoconstrictors. This could be partially explained because of sensitization in protein kinase C and Rho A-Rho kinase Ca^{2+} pathways, which may cause a tendency toward a flaccid stage and modify the responses to NO [51]. All of these mechanisms are further compromised by other factors that impact erectile function including apoptosis or atrophy of the cavernous smooth muscle, due to diminished expression of blc2, intracellular release of Ca^{2+}, increased connective tissue proliferation due to tumor growth factor beta causing fibrosis, and a deficient response to NO in the cavernous and sinusoidal artery, with a decrease in neuronal and endothelial levels of NO synthetase. In brief, there are several components that take place in the endothelial and neural damage in the periphery and central nervous system, which globally impact on ED in patients with DM.

Diabetes is associated with peripheral and autonomic neuropathy and both of these can contribute to ED. The mechanism for ED is due to the reduced or absent parasympathetic activity needed for relaxation of the smooth muscle of the corpus cavernosum, which is produced by the decrease of norepinephrine levels as well as an increase in acectylcholine, resulting in increased NO synthase (NOS) activity, which releases NO.

Other factor is Hypogonadism, associated with type 2 diabetes. One study reported that 20% of diabetic men with ED had frank hypogonadism with a total testosterone level below 8 nmol/L and 31% had borderline low total testosterone levels between 8 and 12 nmol/L. The mechanism of hypogonadism in diabetes is incompletely understood. Hypogonadism is also associated with obesity and advancing age, common factors in type 2 diabetes.

Diagnosis

The International Questionnaire for Erectile Function helps to determine the degree of erectile dysfunction and evaluate the progression or response to medical treatment, one of the questionnaires is the International Index of Erectile Function (IIEF) and its short form, IIEF5 (also known as SHIM: Sexual Health Inventory for Men). The erectile function domain of IIEF and SHIM has been validated to assess the presence and the severity grade of ED. In the erectile function domain of IIEF, men scoring ≤25 are classified as having ED and those scoring >25 are considered not to have ED, with a sensitivity of 97% and specificity of 88%. The SHIM scale, those who score ≤ 21 are considered to have ED and those scoring >21 are considered not to have ED and sensitivity 98% and specificity of 88%.

In certain cases, in which a more precise evaluation of vascular flows is needed, an echo Doppler could be performed to determine cavernous artery flux and morphology. In selected cases, other studies to determine the degree of damage of myelinated pudendal somatosensory fibers and unmyelinated fibers can be done. Additional studies include assessment of nocturnal penile tumescence and electrostimulation. Most of these studies, however, are more commonly used in research protocols than in everyday clinical practice [52].

Treatment

Approximately 20% of patients with ED received pharmacological treatment, for that reason, clinicians should broadly evaluate sexuality among DM patients, trying to improve the sexual activity of patients and consequently their quality of life [40]. Glycemic control is an important factor, a decrease in or maintenance of hemoglobin A1c below 7.0% were significantly associated with a change on IIEF-5.

The first line of treatment are oral medications (phosphodiesterase 5 inhibitors), followed by intracavernosal injection (alprostadil), and finally penile prosthesis.

The daily use of phosphodiesterase 5 inhibitors can improve not only sexual function but also diminishes urinary tract symptoms associated with prostate enlargement. Meta-analysis has confirmed that phosphodiesterase 5 inhibitors are effective treatments of ED in patients with diabetes [53].

Sildenafil citrate, tadalafil, udenafil, and vardenafil hydrochloride are the oral agents for the treatment of erectile dysfunction. All PDE5 inhibitors are less efficacious in

diabetic men. They all share the same mechanism of action, which involves the hydrolysis of guanosine monophosphate to guanosine 5′-monophosphate, diminishing it, causing an increase in the relaxation of the cavernosal smooth muscle mediated by NO, increasing the blood flow into the corpus cavernosum, and causing penile erection [54]. Vardenafil and sildenafil are more effective on an empty stomach and start working after 30 min, with peak action at 1 h and a window of action of 4–6 h. Tadalafil has a long half life with a therapeutic window of 36–48 h, which may aid spontaneity.

Common side effects of phosphodiesterase 5 inhibitors are headache, dyspepsia, bluish eye sight, and facial flushing; lumbar musculoskeletal pain has been found in patients receiving tadalafil and mirodenafil [53]. Phosphodiesterase type 5 inhibitors are contraindicated in those who are on nitrates, because of the potential for a dramatic fall in blood pressure.

Vacuum erection devices cause blood flow to be directed into the penis, and when a satisfactory erection is obtained, a compressive device is applied at the base of the penis in order to prevent blood return and lose the erection. Side effects include cold penis due to noncirculating blood, loss or diminished sensation due to nerve compression, and the uncomfortable process to obtain the erection using the device [55]. External support devices that hold the flaccid penis to allow penetration have been designed, but the use of these instruments has not gained acceptance among patients and their partners.

Another medical option is intraurethral suppositories of prostaglandin E-1 which are injected into the urethra. In men with diabetes, their reported efficiency rate to achieve satisfactory intercourse is 60%, although in clinical practice, they have not proved to be as effective [56, 57]. Injections of prostaglandin E-1 directly into the corpus cavernosum have a direct effect on blood vessels, causing immediate penile erections, with a reported response rate above 83% [58]. Main limitations include the need of injection prior to the sexual encounter, its impact on the spontaneity of sexual intercourse, and adverse effects including penile pain, hematomas, infection, fibrosis and priapism, prolonged and painful erections [59].

Patients not responding to medical therapy, unsatisfied with side effects or patients who prefer a permanent solution should consider a penile prosthesis implant (PPI). PPI improves flaccidity and rigidity, male satisfaction and correlates positively with satisfaction of the sexual partner. The rate of complications related to penile implantation is lower than 5%; they may be catastrophic however and include misplacement, migration, perforation, and a low risk of infection (less than 1.8%) using antibiotic prophylaxis, antibiotic impregnation, or hydrophobic-coated prosthesis [60].

Urinary Tract Infections

Urinary tract infection (UTI) is the most common infection among patients with diabetes mellitus [7, 8], with estimates of diabetics suffering from UTI reaching 10% of patients visiting hospitals [61].

The worldwide prevalence of urinary tract infections (UTI) is around 150 million persons per year [62]. DM patients have a higher incidence of infections in general, and UTI are not the exception. In a cohort of over 6000 patients with diabetes mellitus enrolled into 10 clinical trials of diabetes therapies, the incidence of urinary infection was 91.5/1000 person/years for women and 28.2/11,000 for men. [63]. In the Dutch National Survey of General Practice, patients with Type 1 diabetes mellitus were1.96 times more likely to experience urinary infection and with Type 2 diabetes 1.24 times more likely. [64]. In a recent study of a cohort of 460 hospitalized participants, the overall prevalence of UTI was 27.39% among diabetic patients and 17.83% among nondiabetic participants, with a higher prevalence in ages between 40 and 49 and a higher prevalence between women (43%) in comparison with men (13.8%) [61]. The high prevalence of UTI recorded among the age group 40–49 years could be due to increased rate of sexual activity in this age group. Metabolic abnormalities and long-term complications including neuropathy and nephropathy are presumed to be determinants of increased infectious morbidity [65].

The variety of UTI patients with diabetes ranges from asymptomatic bacteriuria to cystitis, pyelonephritis, renal abscess, xantogranulomatouse pyelonephritis to severe urosepsis [66]. DM is also associated with severe cutaneous infections of the genitals such as Fournier's gangrene.

Asymptomatic bacteriuria is more prevalent in women, due to the anatomical length of the urethra, and it is closer to the warm, moist, vulvar, and perianal areas that are commonly colonized by enteric bacteria [66]. Asymptomatic bacteriuria occurs in 8–26% of diabetic women, a prevalence estimated to be 2–3 times higher than nondiabetic women [67].

DM female patients frequently suffer bacterial cystitis with higher prevalence of both asymptomatic bacteriuria and symptomatic UTI added to recurrent complications, compared to healthy women [62]. Bacterial cystitis is frequently suffered by diabetic patients; it is more common in women than in men, especially in those with type 2 DM. Diabetic women have a higher prevalence of asymptomatic bacteriuria than healthy women, and they have a greater tendency for developing symptomatic UTI and recurrent complications with higher incidence of more serious complications [68, 69]. For women with diabetes and asymptomatic bacteriuria, those with type 2 diabetes have an increased risk for pyelonephritis and subsequent impairment of renal function [68, 69].

Type 2 DM is more than a risk factor for community acquired UTI and is a high predisposition for healthcare associated UTI, such as catheter-associated UTI, postrenal transplant recurrent UTI, and catheter-associated UTI [66]. Hospitalization due to pyelonephritis occurs more frequently in diabetic patients, and they are at higher risk of developing acute pyelonephritis, which could progress to renal abscess, pyelitis or emphysematous cystitis or pyelonephritis, and bacteriemia [66, 70]. In a Canadian report, diabetic women were 6–15 times more frequently hospitalized for acute pyelonephritis and diabetic men 3.4–17 times [71].

A retrospective analysis found that diabetes mellitus was one of four variables independently associated with a poor outcome (clinical or bacteriological failure or relapse) of therapy for acute pyelonephritis. Other evidence supporting increased severity of infection is an increased frequency of bacteremia, more prolonged duration of fever, and increased mortality (12.5% with diabetes and 2.5% without) in older patients with diabetes. Over 90% of episodes of emphysematous pyelonephritis cases occur in persons with diabetes and 67% of episodes of emphysematous csystitis [72]. Other clinical manifestations that are unique or strongly associated with diabetes include abscess formation and renal papillary necrosis.

Pathophysiology

The development of UTI in women is preceded by colonization of the vaginal and periurethral epithelium by the infecting organism. Ascension to the bladder may then ensue E. coli causes the overwhelming majority of UTIs. Normal host defense mechanisms usually prevent entry to or persistence of bacteria within the urinary tract. The growth rate of bacteria and fungi in urine is stimulated by glycosuria [73]. In addition, higher renal parenchymal glucose levels create a favorable atmosphere for multiplication of many microorganisms [66]. A reduction of urinary Tamm Horsfall glycoprotein (THP) excretion which correlates with reduction of renal mass is consistently observed in diabetic nephropathy. Glycation of THP in patients with diabetes or renal diseases also reduces the capacity of THP to inhibit bacterial adherence to human uroepithelium [74].

Bacterial attachment to the uroepithelium is the necessary initiating event permitting bacterial persistence. 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 [75]. A 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. Uropathogenic *E. coli* expressing type 1 fimbriae were twice as adherent to cells from women with diabetes as compared with cells collected from the women without diabetes.

Local urinary cytokines regulate host defence against urinary tract infections. DM results in abnormalities in the host immune defense system that may result in higher risk of developing infection. Immunologic impairments such as defective migration and phagocytes alterations of chemotaxis in polymorphonuclear leukocytes are common in DM patients [76]. A potential risk factor for urinary tract infection is polymorphonuclear leukocyte dysfunction in a high-glucose state. Significantly lower urinary IL-8- and Il-6-concentrations are found in diabetic women compared with nondiabetic controls, and these lower levels correlate with lower urinary leukocyte counts [68, 69]. One recent study shows that monocytes from women with type 1 diabetes produced lower amounts of proinflammatory cytokines upon stimulation with lipolysaccharide, women with diabetes who developed bacteriuria also produced lower urinary IL-6 concentrations, as compared with specimens from bacteriuric control subjects without diabetes [68, 69]. Diminished neutrophil responses, lower levels of cytokines and leukocytes facilitate adhesion of microorganisms to uroepithelial cells and the development of infections [77].

General host factors associated with risk of infection in patients with diabetes include age, metabolic control, duration of diabetes mellitus, microvascular complications, urinary incontinence, and cerebrovascular disease or dementia. The only risk factor associated with acute cistitis in premenopausal women with Type 1 diabetes was sexual activity. Previously suggested as possible risk factors, duration of diabetes or elevated HBA1c levels have not been shown to increase the risk of urinary tract infections in recent studies [68, 69].

The increased frequency of UTI in patients with diabetes might be associated to nerve damage caused by hyperglycemia, affecting the capacity of bladder to sense the presence of urine and leading to stagnation of urine for a long time, or inadequate bladder emptying due to ineffective detrusor contraction, increasing the probability of infections [62]. Over 50% of men and women with diabetes have bladder dysfunction which may impair voiding and facilitate infection. Urinary incontinence is consistently associated with urinary tract infection in diabetic women, but this association is not likely causative. Bladder dysfunction occurs in 26–86% of diabetic women depending on age, extent of neuropathy, and duration of diabetic disease. The possibility that voiding disorders are contributing to UTI should be considered in all diabetic patients.

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. Additionally, urinary infections with Candida

Albicans occur commonly in diabetic women but infrequently in other women.

Clinical Manifestations

UTI in DM patients can be the origin of severe complications that can end up in sepsis, organ failure, and death. Therefore, it is important to be vigilant of the usual clinical manifestations such as urinary urgency, frequency, bad urine odor, pain, dysuria, tenesmus, incomplete emptying and incontinence for lower UTI; and costovertebral angle pain or tenderness, fever, chills for upper UTI [66]. Diabetic patients generally present with symptoms similar to nondiabetic patients, but clinical signs may be altered in some patients with peripheral or autonomic neuropathy. Patients with diabetes are more likely to have more severe presentations of pyelonephritis including fever bacteremia and bilateral renal involvement. Less frequent presentations of urinary infection which occur most often in patients with diabetes include emphysematous cystitis or pyelonephritis, ureteral obstruction secondary to papillary necrosis, and renal or perinephric abscesses.

Diagnosis

Frequent and early screening for UTI should be performed in DM patients with suggestive symptoms, in order to establish the appropriate early treatment and to avoid complications.

As soon as the clinical diagnosis of UTI is suspected, a midstream urine sample must be examined, looking for the presence of leukocytes (more than 10 leukocytes/mm^3) or a positive dipstick leukocyte esterase test to detect pyuria. Microscopic or macroscopic hematuria is sometimes observed [66] associated to positive nitrites and the presence of bacteriuria. A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for every diabetic patient presenting with pyelonephritis or complicated urinary tract infection. Women with symptoms consistent with acute cystitis and who do not have diabetic nephropathy or other long-term complications, particularly if they have a prior history of recurrent acute cystitis, do not usually require a urine culture. However, these women should also have a urine specimen for culture if this is a recurrent episode within 1 month of treatment, if empiric therapy has failed, or if there has been recent antimicrobial treatment so resistant organisms are more likely.

Pyuria is a universal accompaniment of symptomatic urinary tract infection. Thus, the presence of pyuria, by itself, is not useful for diagnosis of urinary tract infection or to differentiate asymptomatic and symptomatic infection. The absence of pyuria, however, is useful to exclude urinary tract infection in patients with questionable symptoms.

A diagnosis of bacteriuria is made when >105 cfu/ml of an organism is isolated from a voided urine specimen. Despite the fact that Escherichia coli is the most frequent bacteria in patients with urinary tract infections, unusual, multidrug resistant and aggressive pathogens are more prevalent in DM patients, including Klebsiella, gram negative rods, enterococci, group B streptococci, Pseudomonas and Proteus mirabilis [78]. Type 2 DM is a risk factor for fungal UTI, such as candida, these patients are more predisposed to be infected by resistant pathogens, including extended-spectrum β-lactamase-positive Enterobacteriaceae, fluoroquinolone-resistant Uropathogens, carbapenem-resistant Enterobacteriaceae, and vancomycin-resistant Enterococci [66].

The increased frequency of serious complications of urinary tract infection in patients with diabetes requires a low threshold for obtaining diagnostic imaging. Ultrasound scanning is safer, less costly, and easier to perform. These methods allowed detection of calculi, obstruction, and incomplete bladder emptying. Computerized tomography (CT) is now accepted as the most sensitive imaging modality for diagnosis and follow-up of abnormalities potentially associated with urinary tract infections. An enhanced CT scan is preferred, but contrast media should be used with caution in patients with diabetes mellitus or with renal disease.

Treatment

Treatment of urinary tract infection in patients with diabetes is generally similar to nondiabetic patients. Key factors to consider include whether the patient is asymptomatic or symptomatic, whether infection is localized to the bladder or kidney, and renal function. Glycemic control is helpful in the control of (UTI) [62].

Assuming that asymptomatic bacteriuria is more common and that the consequences more deleterious among women with diabetes, the question as to whether to attempt to eradicate it is of considerable relevance. In a randomized controlled trial of type 1 and type 2 diabetic women with asymptomatic bacteriuria, women were randomized to treatment with antimicrobials or no treatment for episodes of asymptomatic bacteriuria >3 years. Importantly, the study demonstrated that screening and treatment episodes of asymptomatic bacteriuria had no impact on overall occurrence of symptomatic urinary tract infections or hospitalizations [79]. Therefore there are no short- or long-term benefits for treatment of asymptomatic bacteriuria in women with diabetes mellitus. Asymptomatic bacteriuria by itself is not associated with an increased rate of progression to renal impairment or other long-term complications in patients with diabetes [80].

Acute cystitis in women with good glucose control and without long-term complications should be managed as uncomplicated urinary infection, usually with short-term antimicrobial therapy [81]. However, patients with pyelonephritis and severe systemic symptoms including nausea and vomiting or hemodynamic instability should be hospitalized for initial parenteral antibiotic therapy.

The choice of initial empiric antimicrobial therapy should consider current treatment guidelines, the patient's metabolic status and tolerance, the clinical presentation, and known or suspected local or institutional susceptibility of uropathogens (Table 59.1). The use of trimethoprim, cotrimoxazole, or nitrofurantoin is considered as the standard regimen of antibiotic therapy [82]. Broad spectrum cephalosporins and fluoroquinolones are the drugs of choice for pyelonephritis. However, alternate regimens such as the carbapenems meropenem, ertapenem or doripenem or betalactam/beta lactamase inhibitors such as piperacillin/ tazobactam or ampicillin/sulbactam may be appropriate if antimicrobial resistance is a concern. For patients who present with severe sepsis or septic shock, broad spectrum antimicrobial therapy to provide maximal coverage for resistant organisms should be initiated pending urine culture results. Antimicrobials with nephrotoxic side effects, e.g., aminoglycosides should be used with caution in patients with renal insufficiency. Nitrofurantoin should be avoided in renal failure as drug metabolites accumulate and may cause peripheral neuropathy [83]. There are studies reporting higher frequency of extended spectrum beta-lactamase producing E. coli and Klebsiella pneumonia in diabetic patients. However, these studies didn't report whether diabetes was an independent risk factor for increased resistance [84].

Table 59.1 Recommendations for antimicrobial therapy in uncomplicated cystitis in patients with diabetes mellitus

Antimicrobial	Regimen	Duration
First-line		
Fosfoycin trometamol	3000 mg	Single dose
Nitrofurantoin	50–100 mg orally 3–4 times a day	5 days
Nitrofurantoin monohydrate/ macrocrystals	100 mg twice a day	5 days
Trimethoprim/ sulfamethoxasole	800/160 mg orally every 12 h	3 days
Alternatives		
Ciprofloxacin	250–500 mg orally every 12 h	3 days
Levofloxacin	250–500 mg every 12 h	3 days
Norfloxacin	400 mg orally every 12 h	3 days
Ofloxacin	200 mg orally every 12 h	3 days
Cephalexin	500 mg 4 times daily	7 days
Axetil cefuroxime	500 mg twice daily	7 days
Cefpodoxime proxetil	100 mg orally every 12 h	3 days
Cefixime	400 mg daily	3 days

Among women with type 1 diabetes, sexual activity has been identified as the most important risk factor for the development of urinary tract infections, similar to women without diabetes. Continuous or postcoital prophylaxis with low-dose antimicrobial agents and intermittent self-treatment with antimicrobials are the recommended strategies to prevent recurrent urinary tract infections in women without diabetes which also could be useful in women with diabetes [85].

Recurrent infection in young women without long-term complications of diabetes is managed as acute uncomplicated cystitis, including antimicrobial therapy given as long-term low dose or post intercourse prophylaxis for women with very frequent recurrence. For patients with complicated infection, it is essential to identify and correct any known urologic abnormalities and to optimize voiding, including use of intermittent catheterization where appropriate.

Conclusions

Patients with diabetes are highly susceptible to urologic complications. They may be serious, life threatening, and affect quality of life. The underlying mechanisms determining the increased risk and severity of infection are not fully described, but alterations in specific components of the host response, metabolic abnormalities, and long-term complications of diabetes likely contribute. It is important to take into account these comorbidities in the management of diabetes and to understand their pathogenesis to prevent systemic dissemination. Many patients with diabetes accept these comorbidities are part of their disease but clinicians should be aware, interrogate, and screen for these complications in order to indicate the adequate treatment. Controlled clinical trials of therapy comparing patients with and without diabetes mellitus or diabetic patients stratified by adequacy of control and complications will be necessary to improve management of this common and important problem.

Multiple Choice Questions

1. Urologic complications in people with diabetes are associated to:
   (a) Nerve function disturbances
   (b) Loss of innervations of neuromuscular terminals
   (c) Abnormal immune responses
   (d) Altered sympathetic/parasympathetic innervations
   (e) **All of the above**
2. Peripheral accumulations of fat in the abdominal region of DM patients have been associated to an increased risk of urologic complications including:

(a) **Urinary incontinence**
(b) **Erectile dysfunction**
(c) **Benign prostatic hyperplasia**
(d) **Urinary tract infections**
(e) **Cancer**

3. Diabetic cystopathy is characterized by:
(a) **Urinary incontinence**
(b) **Increased post voiding residual volume**
(c) **Urinary tract infection**
(d) All of the above
(e) None of the above

4. Bladder symptoms of diabetic cystopathy include:
(a) **Polyakiuria**
(b) Decreasing caliber and strength of the voiding flow
(c) Terminal dribbling
(d) **Urgency incontinence**
(e) High postvoid residual urine

5. Infiltration of the detrusor muscle can be achieved with:
(a) Oxybutynin
(b) Solifenacin
(c) **Botulinum toxin**
(d) Darifenacin
(e) Tolterodine

6. Positive predictive predictors of benign prostatic hyperplasia:
(a) Urinary tract infection
(b) Plasma insulin levels
(c) Dysuria
(d) **Urinary urgency**
(e) Fasting blood glucose

7. Patients with benign prostatic hypertrophy and enlarged prostate should be treated with:
(a) Nonselective alpha-1 blockers
(b) Selective alpha-1 blockers
(c) Alpha reductase inhibitors
(d) **Alpha-1 blockers combined with 5 alpha reductase inhibitors**
(e) Surgical management is the only option

8. The reported prevalence of sexual dysfunction in men with type 2 diabetes:
(a) 18%
(b) 37%
(c) **46%**
(d) 53%
(e) 71%

9. The reported prevalence of sexual dysfunction in women with type 1 diabetes:
(a) 18%
(b) 37%
(c) 46%
(d) 53%
(e) **71%**

10. Erectile dysfunction:
(a) is a minor complaint of men with diabetes
(b) has not been quantified
(c) is usually present at diagnosis
(d) **is the third most common chronic complication and the most significantly affecting quality of life**
(e) is common but less relevant regarding quality of life

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