FEATURE ARTICLE

Managing Sexual and Reproduction Complications of Diabetes in Men

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Male reproductive disorders are a less discussed complication of diabetes. These disorders can include balanitis, erectile dysfunction, decreased libido, erectile impotence, and infertility. This article reviews the epidemiology, pathophysiology, classic presentation, and treatment of balanitis, erectile dysfunction, and sperm dysfunction.

There are many medical conditions that affect the penis secondary to diabetes. Balanitis, erectile dysfunction (ED), and infertility are the common sexual and reproductive diagnoses secondary to diabetes and will be described in this article, with recommendations for treatment. The risk of developing these disorders can be mitigated by lifestyle changes that incorporate regular physical activity, a healthy diet that includes various fruits and vegetables, and even early diabetes recognition and management. The case studies below depict three commonly experienced complications of the testes and penis among individuals with diabetes.

Case 1: Balanitis

A 48-year-old cisgender male presents to the primary care clinic with complaints of burning and itching of the penis. The patient has a history of type 2 diabetes for which he takes only metformin (A1C 7.5% 1 month ago) and gastroesophageal reflux disease. He reports no other relevant medical history. The patient's BMI is 35 kg/m^2, and his vital signs are within normal limits. He has a random blood glucose level of 256 mg/dL. On physical examination, he is uncircumcised, with erythema and white, curdy discharge of the foreskin and glans. What is the most likely diagnosis?

Background

Balanitis is an inflammation of the glans penis that affects ∼3–11% of individuals with a penis during their lifetime (1). One of the most common fungal causes of balanitis is the yeast *Candida albicans* (1). Although this microbe is part of the physiologically normal flora found on the penis, diabetes causes an imbalance of microbe growth, allowing overgrowth of *C. albicans* leading to balanitis.

Patients typically report pain and irritation on the glans penis, discharge, and dysuria. Patients could also present with phimosis (inability to retract foreskin over glans penis) or paraphimosis (inability to move foreskin from a retracted position over the glans penis, potentially causing a tourniquet-like effect). Differential diagnosis for balanitis includes consideration of sexually transmitted infection, eczema, psoriasis, dermatitis, and genital cancer (1).

Epidemiology

Balanitis can occur at any age and affects a high number of individuals with an uncircumcised penis—up to 1 in 30—during their lifetime (1). There are numerous risk factors for balanitis, including poor personal hygiene, morbid obesity, uncircumcised penis, human papilloma virus, and diabetes.

Individuals who experience frequent hyperglycemia are especially prone to balanitis because of the excess glucose excreted in the urine. The glucose in the urine interacts with the normal skin habitant on the glans of the penis, enabling fungal or bacterial growth. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are one of the most effective drugs for the treatment of type 2

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diabetes (2) that lower glucose by regulating renal tubular glucose. However, through a glucose resorption inhibition mechanism, they cause an increase in the elimination of glucose in the urine (2). As a result, the U.S. Food and Drug Administration issued a warning that this drug class may cause serious genital and urinary tract infections in people with type 2 diabetes (3). The results of one study revealed an incidence rate of 4–6% for bacterial and fungal infections with the use of SGLT2 inhibitors compared with 1% with placebo (3). Educating patients on the possible side effects and complications of SGLT2 inhibitor therapy will facilitate early management of any symptoms they may develop.

Possible Presentation

Symptoms of balanitis are patient dependent and vary based on acuity. They may include unpleasant smell, painful urination, pain on the glans, and pruritis (1). Physical exam findings of balanitis may include tight, shiny skin on the glans; redness around the glans; femoral lymphadenopathy; lesions on the penis; inflammation and irritation of the glans; and a thick, cheesy, white discharge under the foreskin.

Diagnostics/Laboratory Tests

Definitive diagnosis of balanitis is achieved through microscopy identification of budding yeast or pseudohyphae using a potassium hydroxide preparation.

Treatment

Treatment of balanitis is multimodal, but glycemic control is the main focus for people with diabetes. Topical azole antifungals (e.g., clotrimazole 1% twice daily or miconazole 2% twice daily) for 1–3 weeks is the treatment of choice (4). Treatment is typically focused on local hygiene measures and/or empirical antifungal treatment (4). For patients with more severe symptoms, a single dose of oral fluconazole 150 mg or itraconazole 200 mg twice in 1 day is appropriate (4). If the patient has foreskin, an option to prevent recurrent infections may be urological consultation for circumcision (1). In addition, barrier creams such as petroleum ointment, zinc oxide, and coconut oil can prevent irritation from glucose leakage when using SGLT2 inhibitors for diabetes management.

Case 2: ED

A 67-year-old cisgender male with type 2 diabetes, hypertension, and hypercholesterolemia presents to his primary care physician. He is in a new relationship and reports that he is unable to achieve and maintain an erection during intercourse. What considerations should be addressed at this time?

Background

ED is the inability to get sufficient penile erection for and during sexual intercourse (5). Table 1 depicts risk factors that make a person more susceptible to erectile dysfunction. Additionally, as depicted in Table 2, primary care medications used to treat diabetes comorbidities can affect patients' libido.

Autonomic neuropathy is the primary cause of ED in men with diabetes; it can lead to loss of autonomic nerve-mediated relaxation to the corpus cavernosum, which is essential for penile erections (6). Additionally, an increase in atherosclerosis secondary to diabetes can limit blood flow into the corpus cavernosum.

Despite these established risks and correlations, ED often remains undiagnosed because of stigma (7). Some patients may feel embarrassed to admit they have ED. If the patient is reluctant to receive advice because of emotional and psychological factors, this reluctance may delay treatment and worsen their complications over time.

Alternatively, health care practitioners may not inquire about sexual activity or ED. Health care practitioners can normalize this medical condition by asking patients open-ended questions regarding their sexual activity. By identifying these risk factors and associated symptoms early, we can optimize psychosocial support and treatment for patients.

Epidemiology

Diabetes is linked to the development of ED. Almost half of cisgender males with type 1 or type 2 diabetes

TABLE 1 Risk Factors for ED

Risk factors for ED include:

- Advancing aging
- Alcohol use
- Cardiovascular disease
- Cigarette smoking
- Diabetes
- Hypercholesterolemia/atherosclerosis
- Hypertension
- Illicit drug use
- Medications
- Neurological conditions: dementia, multiple sclerosis, Parkinson's disease
- Peyronie's disease
- Prostate cancer and status post prostatectomies
- Psychological conditions: depression, anxiety
- Trauma

Adapted from ref. 5.

TABLE 2 Medications That May Cause ED

Medications Associated With ED	Common Drugs or Drug Classes
Antihypertensives/diuretics	Hydrochlorothiazide, furosemide, β-blockers, calcium channel blockers, and α-blockers
Anti-Parkinson's agents	Bromocriptine and levodopa
Analgesics: opioids	Hydrocodone, oxycodone, and morphine
Antidepressants	Lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants
Antihistamines	Diphenhydramine, dramamine, hydroxyzine, and promethazine
Cytotoxic agents	Methotrexate
Sedative hypnotics	Benzodiazepines
Illicit drugs, alcohol, and nicotine	Cocaine, heroin, and marijuana
Hormones and hormone-active agents	α-Reductase inhibitors, androgen receptor blockers, androgen synthesis inhibitors, corticosteroids, estrogens, gonadotropin-releasing hormone analogs, and progesterones
Antipsychotics	Chlorpromazine, haloperidol, pimozide, thioridazine, and thiothixene

Adapted from ref. 5.

will experience ED within 10 years of their diabetes diagnosis, representing a more than threefold probability of developing ED compared with individuals without diabetes (8). Compared with men without diabetes, men with diabetes have increased odds of experiencing ED (odds ratio 3.62, 95% CI 2.53–5.16, $P < 0.0001$) (9). ED prevalence estimates among men with diabetes range from 27 to 75% depending on age (10). Other risk factors for ED include comorbid atherosclerotic cardiovascular disease (CVD), hypertension, chronic kidney disease, and peripheral neuropathy (10,11).

Classic Presentation

Individuals experiencing ED may present with complaints of lack of or decreased libido, inability to achieve and/or maintain an erection during intercourse, loss of morning erection, and lack of ejaculation (12).

Neurological, cardiovascular, and urogenital systems should be the focus of the physical exam. If a neurogenic origin for ED is suspected, the exam should include checking the reflective arc sacral parasympathetic nervous system (S2–S4), perineal sensitivity, anal reflex, and bulbocavernosus reflex (13). Because ED may be associated with atherosclerosis, individuals with ED should be screened for CVD, and their risk should be stratified (14).

Table 3 depicts the cardiovascular risk stratification for people with ED based on the Princeton III consensus recommendations (15,16). Individuals with intermediate risk should undergo stress testing, with referral cardiology as necessary; those at high risk should be evaluated by a cardiologist (15,16).

Finally, urogenital causes of ED to consider include varicoceles, hypospadias, and Peyronie's disease (17). If any of these are suspected, further diagnostic studies and evaluation by a urologist should be considered before treatment is initiated.

Diagnostics/Laboratory Tests

The work-up for psychogenic, neurogenic, hormonal, and anatomical ED etiologies is discussed below and summarized in Table 4.

Given the high incidence of depression and anxiety in patients with ED, these individuals should be screened with validated instruments such as the Patient Health Questionnaire-9 (PHQ-9) and the general anxiety disorder-7 (GAD-7) instruments to support a secondary or contributing diagnosis of anxiety and depression. Stress in coping with diabetes can be associated with ED and can be identified through the use of tools such as the 20-item Problem Areas in Diabetes (PAID) scale to patients for diabetes distress (18).

In the process of making a definitive psychogenic etiology, it may also be useful to use a nocturnal monitoring tumescence (NPT) test to measure the number and

TABLE 3 CVD Risk Stratification in People With ED Based on Princeton III Consensus Recommendations (15)

Characteristic	Low-Risk Category	Intermediate-Risk Category	High-Risk Category
Symptoms	Asymptomatic	Symptomatic	
Risk factors for coronary artery disease (excluding sex), *n*	<3	>3	
Angina history	–	Mild or moderate stable angina	Unstable angina
History of myocardial infarction	–	≥2 weeks ago	Within the past 2 weeks
New York Heart Association classification	Class I or II	Class III	Class IV
Valvular disease	Mild	Moderate to severe	
Hypertension	Controlled	Uncontrolled	
Miscellaneous other factors	Post successful coronary revascularization	Noncardiac sequalae of atherosclerotic disease (e.g., peripheral vascular disease and stroke)	Hypertrophic obstructive and other cardiomyopathies

duration of erections and their degree of rigidity (19). Normal findings would include three to five erections every 8 hours of sleep, with a mean erection duration of 30 minutes and a maximal rigidity >70% (19). The NPT can assist in differentiating psychological from physiological causes of ED.

Individuals with hypogonadism also may present with ED. Symptoms of hypogonadism include decreased sexual drive, depressed mood, fatigue, and ED. An initial screening for hypogonadism can be accomplished with measurement of the serum testosterone level (5). It would be appropriate to initiate testosterone replacement therapy and to also test for luteinizing hormone (LH) and follicle-stimulating hormone (FSH) if low testosterone levels are identified (5). Laboratory testing that reveals a low LH level and a high prolactin level may indicate a disorder of the hypothalamic pituitary axis (5). Patients who are suspected to have pituitary disorders should be considered for MRI of the brain.

TABLE 4 Clinical Recommendations for ED Etiologies

Etiology	Clinical Recommendation
Psychogenic	PHQ-9, GAD-7, and PAID assessment instruments and NPT test
Neurogenic	Physical exam
Hormonal	Serum testosterone, FSH, LH, and prolactin levels
Anatomical	CIS test and color Doppler ultrasound

CIS, combined intracavernous injection and stimulation.

Treatment

Because the etiology of ED is multifactorial, treatment for an unknown pathophysiology proves to be difficult. The confounding factor of diabetes to ED exponentially complicates treatment options because certain pathologies of diabetes-induced ED are irreversible. In its *Standards of Medical Care in Diabetes* guidelines, the American Diabetes Association recommends that all people with diabetes should also receive risk factor modification for atherosclerotic CVD through lifestyle modification, blood pressure management, statin therapy, smoking cessation, and, if appropriate, antiplatelet agents (20).

Useful tools such as the International Index of Erectile Function (IIEF; Supplementary Table S1) are helpful to measure sexual function (21). There are five categories based on the IIEF score: severe (score of 5–7), moderate (score of 8–11), mild to moderate (score of 12–16), mild (score of 17–21), and no ED (score of 22–25). This test should be used over a period of time to monitor symptoms and will be given at the initial evaluation.

The phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil, vardenafil, and avanafil are the mainstay of oral medical treatment of ED (5,22). Table 5 depicts contraindications to these medications, which include concomitant use of nitrates, guanylate cyclase

TABLE 5 Overview of PDE5 Inhibitors for the Treatment of ED

Medication	Instructions	Onset of Action, minutes	Duration of Action, hours	Contraindications and Clinical Concerns
Sildenafil	Take 50 mg on an empty stomach by mouth 1 hour before sexual activity	30–60	4	• Hypersensitivity • Pulmonary veno-occlusive disease
Tadalafil	Take 10 mg 1 hour before sex or 2.5 mg by mouth daily	30–60	Up to 36	• Hypersensitivity • Pulmonary veno-occlusive disease • CrCl <30 (for ED or benign prostatic hyperplasia)
Avanafil	Take 100 mg 15 minutes before sexual activity	15–30	Up to 3–5	• Hypersensitivity
Vardenafil	Take 10 mg 60 minutes before sexual activity	60	8	• Hypersensitivity • Prolonged QT interval • Hereditary fructose intolerance • High-fat meals reduce peak concentration

CrCl, creatinine clearance.

stimulators, or α-blockers, which can lead to hypotension. This drug class should be avoided in patients with a history of hypersensitivity reactions to these drugs (22). Individuals with hypertension, coronary artery disease, alcohol abuse, smoking, hypotension, or other cardiac diagnoses should be evaluated before prescribing these medications.

For patients in whom PDE5 inhibitors fail and those in whom these drugs are contraindicated, other treatment options include vacuum erection devices and local administration of vasoactive medication via a urethral suppository or intracorporal injection (22). Penile prostheses and penile vascular regeneration is a more invasive, but viable, option for patients with irreversible damage of the erectile mechanism (22).

Case 3: Infertility

A 44-year-old cisgender male with type 2 diabetes presents to the clinic with concerns regarding infertility. The patient and his 35-year-old cisgender female partner report difficulty with conceiving after 7 months of trying. Neither partner has had prior pregnancies. What evaluations should the provider recommend?

Background

Male reproductive disorders may affect all aspects of a patient's life, including physical, psychological, social, and sexual well-being. Studies of semen count, motility, concentration, volume, and morphology have yielded conflicting results, and no single consistent abnormality explains a higher incidence of infertility (22). A 2021 meta-analysis of 44 studies, which included 20,367 men with obesity and 1,386 men with diabetes, identified that both obesity and diabetes negatively affect sperm parameters and are associated with lower testosterone levels (23).

Epidemiology

Male-factor infertility is described as an alteration in sperm concentration and/or motility in one of two sperm collections (24). Male-factor infertility is found in 40–50% of all infertility cases and affects 7–12% of the global male human population (24). The actual prevalence of infertility in men with type 2 diabetes and obesity is unknown (23). In a primary care–based study of Qatari men with type 2 diabetes ($n = 857$), the rate of infertility was >35% (25). However, more studies are needed to estimate the prevalence globally.

Diagnostics/Laboratory Test

Because of the complex nature of narrowing down the specific etiology of male infertility, laboratory testing such as a hormone assay and semen analysis are indicated (12). A hormone assay should include prolactin, both plasma and urinary FSH and LH, testosterone, and free testosterone. A semen analysis should include quality of motility, seminal fluid volume/ejaculation, sperm concentration, sperm morphology, and total sperm number.

Individuals with diabetes have lower sperm motility and a lower percentage of normal sperm compared with people without diabetes (26). Research indicates

that these findings may be the result of insulin playing a prominent role in the regulation of the anterior pituitary cells (26).

Treatment

Individuals experiencing infertility should be referred for specialty evaluation after 12 months of trying to conceive if the cisgender female partner is <35 years of age (25). If the partner is ≥35 years, a more expedited referral should occur after the couple has tried for 6 months to conceive (27).

There are many treatment options for infertility. Treatments focus on the primary cause but mainly include medication therapy, behavioral therapy, surgery, artificial insemination, and assisted reproductive technology (27). These therapies should be implemented as soon as possible to achieve desirable affects.

The most common form of assisted reproductive technology is in vitro fertilization, which is a treatment option for retrograde ejaculation, decreased sperm count or motility, and unexplained infertility (28). There are no absolute contraindications to the procedure (28). Patients who are unsuccessful in their diabetes treatment plans and have infertility complications should be educated and offered this procedure to improve their physical, psychological, social, and sexual health.

Conclusion

Diabetes can affect men's health in specific ways that include balanitis, ED, and infertility. A heightened awareness of these conditions on the part of clinicians is required. Clinicians must be able to appropriately identify and treat balanitis, screen for ED (a common and under-reported condition), and perform a workup for infertility, referring to specialists when necessary. Underpinning all of these conditions is high-quality prevention and treatment of diabetes and the comorbidities that are often associated with both physical and psychological outcomes.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

J.L. and K.R. researched data and wrote the manuscript. J.M. researched data and wrote and reviewed/edited the final manuscript. J.M. is the guarantor of this work and, as such, takes responsibility for the integrity of the literature review and analysis.

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