Chapter 26
Male Sexual Dysfunction in Diabetes Mellitus

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Introduction

Male sexual dysfunction can be classified according to the following categories: erectile dysfunction (ED), orgasmic, ejaculatory dysfunction, priapism, and decreased libido. Of these various disorders, medical therapy for ED is the most advanced. ED, also known as impotence, is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual function.[1] In recent years, there has been an escalating public awareness of the magnitude of ED, partly attributable to the advent of Viagra™, Levitra™, and Cialis ™ and their associated marketing. The impact of ED is significant as its prevalence in men aged 40–70 years old was estimated at 52% by the Massachusetts Male Aging Study. Based on these data and the US population projection for the year 2020 of more than 62 million men 45–84 years old, ED will affect more than 31 million men and millions more over the age of 84.[2,3] The projected worldwide prevalence of ED for the year 2025 will be staggering at 322 million men.[4] Certain patient populations are found to have a significantly higher prevalence of ED; for example, diabetic men have a more than threefold increase in risk of ED compared to their nondiabetic counterparts. Indeed, diabetes mellitus is the single most common cause of ED.[5] More than 50% of diabetic patients are afflicted with some degree of ED, and approximately 50% of the patients evaluated at our Center for Male Sexual Dysfunction are diabetic.

Studies have found ED to be an age-dependent disease process that is accelerated in age-matched diabetic men. The prevalence of ED in diabetic men ranges from 35 to 75%,[3] and correlates positively with patient age, duration of diabetes, and disease severity. Compared to healthy men, the onset of ED occurs 10–15 years earlier on an average in diabetic men, regardless of insulin dependency status.

Etiology

ED is multifactorial in origin, but can be classified as either organic or psychogenic.[6] Organic ED can be secondary to vasculogenic, neurogenic, hormonal, or cavernosal smooth muscle abnormalities. Psychogenic ED is a result of central nervous system inhibition of the erectile mechanism and is most prevalent in younger men. The common causes of the organic component of ED in men with diabetes are autonomic neuropathy and vascular abnormalities. The latter are often associated with diabetes, reflecting disease in major arteries, arterial insufficiency, veno-occlusive dysfunction, and microvascular abnormalities.[7–11] Corporal cavernosal smooth muscle (CCSM) abnormalities, such as enhanced CCSM tone, are also essential factors in diabetes-induced ED. Chronic renal failure and endocrine disorders such as hypogonadism, hyperprolactinemia, hypothyroidism and hyperthyroidism, testicular failure, and estrogen excess may also result in ED. Substances of abuse and certain medications, such as antihypertensives, antidepressants, hormones, diuretics, and cardiac medications, are

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L. Poretsky (ed.), *Principles of Diabetes Mellitus*, DOI 10.1007/978-0-387-09841-8_26,

commonly associated with ED.[6–10] Cummings et al. describe the striking degree of overlap between the risk factors of ED and common comorbidities of diabetes: cardiovascular disease, treated and untreated hypertension, multiple drug therapy, neuropathy, and obesity.[12] Thus the vulnerability of diabetic men to ED is further compounded by their additional need for multiple medications for other diabetes-associated medical conditions. Finally, trauma, irradiation, or pelvic surgery can also result in iatrogenic ED. Table 26.1 summarizes the various processes that contribute to ED.

Table 26.1 Etiology of erectile dysfunction

Systemic diseases	*Penile*
Diabetes mellitus	Peyronie's disease
Atherosclerosis	Epispadias
Arterial hypertension	Priapism
Mycocardial infarction	
Scleroderma	*Psychiatric*
Renal failure	Depression
Liver cirrhosis	Widower's syndrome
Idiopathic hemochromatosis	Performance anxiety
Neurogenic	*Nutritional*
Epilepsy	Protein malnutrition
Cerebrovascular accidents	Zinc deficiency
Multiple sclerosis	
Guillain–Barre	*Hematologic*
Alzheimer's disease	Leukemias
Respiratory	
Chronic obstructive pulmonary disease	*Infections*
	Brucellosis
Endocrine	Tuberculosis
Hyperthyroidism	AIDS
Hypothyroidism	Trypanosomiasis
Hypogonadism	

General Penile Erection Physiology

The presentation of diabetic ED can be described in one of three ways: (1) asymptomatic diabetes followed years later by impotence, (2) impotence as a firm sign of diabetes, and (3) temporary impotence resulting from poorly controlled diabetes, which is more likely caused by associated malnutrition and weakness.[13] The onset of organic ED is usually insidious and gradual, initially presenting with the inability to sustain erection, followed by incomplete rigidity and ultimately complete loss of erectile function. In order to appreciate the penile erectile physiology and dysfunction, knowledge of the penile anatomy and hemodynamics of erection is imperative.

The penis originates as separate, paired structures, the crura, which are attached by dense facial fibers to the periosteum of the ischiopubic rami. As the crura course toward the pubic symphysis, they join together and to the corpus spongiosum caudally to form a tripartite structure. The corpora cavernosa are enclosed in a thick fibrous sheath, the tunica albuginea, whose fibers unite medially to form a perforated septum that allows the two bodies to function as a single unit. At the cellular level, the cavernosal tissue contained within the corpora contains a meshwork of interconnected cavernosal spaces known as sinusoidal or lacunar spaces. These are lined by vascular endothelium and separated by trabeculae composed of bundles of CCSM fibers with an extracellular matrix of collagen, elastin, and fibroblasts. Gap junctions, hexamer protein-lined aqueous intercellular channels, connect the CCSM cells and create an efficient syncytial network of those smooth muscle cells.[10–14]

The arterial inflow to the penis is the end terminal of the internal pudendal artery, a branch of the hypogastric or internal iliac artery. Upon emerging from Alcock's canal, the internal pudendal artery gives rise to the common

penile artery, which further subdivides into the bulbo-urethral, cavernosal (deep), and dorsal penile end arteries. The cavernosal arteries of the penis give off multiple helicine branches that are tortuous and contracted in the flaccid state and become straight and larger in caliber during erection. While the vascular elements lead to tumescence, it is the intracavernosal pressure that ultimately determines erectile function.

The penis is a complex vascular organ that requires the coordination of vascular, neural, and hormonal factors in order to achieve satisfactory penile erection. Any abnormality that affects the integrity of the penile vasculature may result in ED. Four physiologic mechanisms are necessary to effect penile erections: (1) an intact neuronal innervation, (2) an intact arterial supply, (3) appropriately responsive CCSM with normally functional intercellular communication, and (4) an intact veno-occlusive mechanism. Nonetheless, penile erection and detumescence are principally vascular events coordinated by the relaxation and contraction of CCSM, respectively. In the absence of severe arterial insufficiency, relaxation of the CCSM is sufficient to elicit a sustained erection.[15,16] The CCSM tone is thus a primary determinant of erectile function. In the flaccid state, the cavernosal arteries and cavernosal smooth muscle cells are constricted, permitting venous outflow. In the flaccid state, blood flow via the cavernous arteries into the cavernous spaces is minimal (3–5 mL/min). Sexual stimulation leads to a decrease in peripheral resistance, vasodilation, and a tenfold increased blood flow through the cavernous and helicine arteries. The intracavernous pressure increases without any accompanying increase in systemic pressure. Relaxation of the trabecular smooth muscle causes increased compliance of the cavernosal spaces, leading to penile engorgement and erection. In the fully erect state, compression of the trabecular smooth muscle cells against the fibroelastic tunica albuginea causes closure of the draining emissary veins and accumulation of blood at systemic pressure in the corporal sinusoidal bodies. Detumescence ensues during contraction of the trabecular smooth muscle, with resumption of arterial blood flow at the prestimulation level and reopening of venous outflow channels. The intracavernosal pressure declines leading to the flaccid state. Any interruption or interference in this cascade of vascular events may precipitate ED.[10,17,18]

Pathophysiology of Erectile Dysfunction and Diabetes

Neurological/Biochemical Physiology

The Physiological Problem

The normal state of the penis is flaccidity, i.e, contracted. ED is the inability to achieve sufficient blood flow and relaxation of the CCSM to raise the corporal pressure to mean systemic levels for a prolonged duration. In men with diabetes who have impaired erection, there is the inability to either obtain or maintain a state of penile rigidity sufficient for satisfactory intercourse.

Neurological Changes

The neurotransmitters that mediate penile contraction include noradrenaline and the endothelins. There is a long-standing view that ED in men with diabetes is primarily caused by neurological abnormalities.[7,19,20] Ellenberg attributed the increased incidence of diabetic impotence to autonomic neuropathy.[7,8] Penile erection is under the regulation of the autonomic system. The neurotransmitters that control erection can be grouped into those that mediate contraction (noradrenaline, the endothelins, neuropeptide Y (NPY), prostanoids, angiotensin II, and the RhoA/Rho-kinase system) and those that mediate relaxation (acetylcholine, nitric oxide, vasoactive intestinal polypeptide, calcitonin gene-related peptide, adrenomedullin, adenosine triphosphate (ATP), adenosine, and the prostanoids). Sexual stimuli result in neurological impulses via somatic and autonomic motor tracts to the penis, generating tumescence and erection. Recent studies suggest that the motor control of erection is exerted via both sympathetic and parasympathetic nerve fibers, and that neither a cholinergic nor an adrenergic neurotransmitter system is solely responsible for erectile function. Interestingly, intravenous or intracavernous injection of atropine fails to inhibit penile erection.[21] Moreover, in vitro experiments on human erectile tissue treated with exogenous acetylcholine have demonstrated contraction or relaxation, or no responses at all.

Saenz de Tejado et al. suggest that acetylcholine is probably an inhibitory modulator of adrenergic constrictor nerves and a facilitatory modulator of nonadrenergic noncholinergic relaxation.[22] Studies from Blanco et al. demonstrated an impaired ability of penile cholinergic nerves from impotent diabetic men to synthesize and release acetylcholine. Therefore, they concluded that these patients have dysfunctional penile cholinergic nerves and that this autonomic neuropathy within the corporal tissue worsens with disease duration.[20]

Studies have also suggested a role for adrenergic neurotransmitters in erectile function. High concentrations of norepinephrine have been demonstrated in the blood vessels and CCSM in healthy men. These are significantly decreased in impotent diabetic patients.[23] Animal experiments show that the sympathetic noradrenergic fibers innervating the penis appear to demonstrate neuropathic changes and markedly reduced norepinephrine content in uncontrolled streptozotocin-induced diabetic rats supporting the finding in human studies that noradrenergic sympathetic nerve damage in the penis is a complication of diabetes.[24–27] Our studies also demonstrate that alterations in α-adrenoceptor (phenylephrine) responsiveness are positively correlated with age in diabetic human erectile tissues but not in nondiabetic tissues.[28] However, in an animal model of type 1 diabetes we found that there was no significant alteration in the amount of force produced in response to phenylephrine compared to controls.[29] Nonetheless, it has been observed that the addition of β-adrenergic blockers to isolated corporal tissue strips has no apparent effect on the contractile response to catecholamines, indicating that CCSM relaxation cannot be effectively achieved solely by endogenous catecholamines.[18]

Since neither cholinergic nor adrenergic mechanisms can fully mediate erectile function, the role of nonadrenergic and noncholinergic neurotransmitters (NANC) has been explored. One of the peptides that has been studied as a neurotransmitter in penile physiology is vasoactive intestinal polypeptide (VIP). A potent vasodilator contained in the neurons of the major pelvic ganglion, VIP-immunospecific fibers have been demonstrated in cavernosal tissue.[30] Experiments have demonstrated a dose-dependent relaxation response to VIP,[31] and VIPergic nerves have been found to be depleted in the corpora of diabetic men.[32] Additional data demonstrate a consistent reduction of VIP-like immunoreactivity density in penile disease from streptozotocin-diabetic rats and human diabetic penile tissue when compared with control subjects.[33] Lincoln et al. utilized an immunohistochemical, histochemical, and biochemical investigation of the VIPergic, cholinergic, and adrenergic innervation in penile tissue from impotent patients and provided evidence that all three types may be affected in diabetes.[34]

Endothelial cell-derived modulators, such as endothelin-1 (a potent vasoconstrictor peptide), nitric oxide, and prostanoids, have been identified in the corpus cavernosum.[35,36] Endothelin is one of the most potent vasoconstrictors known. The endothelins (ETs) are a family of 21-amino acid peptides and include ET-1, ET-2, and ET-3,[37] each the product of a separate gene and differing from one another by only a few amino acids.[38] Relative expression of the ET isoforms varies in different tissues with the biological actions of the ETs being determined by their relative binding to ET receptor subtypes.[39] ET-1, the most well characterized and predominant ET in normal plasma,[40] is synthesized by endothelial cells,[37] including corpus cavernosal endothelial cells[36] and CCSM cells.[41] These observations along with the presence of specific binding sites for ET-1 on human CCSM cells, the effect of ET-1 on intracellular calcium levels, and the long-lasting and potent contractile effects of ET-1 on human CCSM strips suggest that ET-1 may serve as a crucial modulator of ED.[42]

Endothelin levels in plasma are elevated in the diabetic state in experimental animal models of both type 1[43] and type 2 diabetes.[44] ET-1 levels are also elevated in diabetic humans. A recent study by Shestakova et al. showed a significant increase in plasma endothelin levels in type 1 diabetic patients. The level of endothelin in the plasma correlated positively with the severity of renal disease.[45] Mokdad et al. reported elevated endothelin levels in type 2 diabetes patients.[46] Data from Francavilla et al. also reveal elevated circulating ET-1 levels in diabetic and nondiabetic men with ED compared with normal men. They also showed elevated ET-1 levels in diabetic impotent patients when compared with nondiabetic impotent individuals, suggesting that diffuse endothelial dysfunction contributes to diabetic ED.[53]

The two main subtypes of ET receptors are referred to as ETA and ETB and are encoded by separate genes.[47,48] Activation of one ETB receptor isoform has been shown to cause a transient vasodilation[49] while activation of either the ETA or the alternative ETB receptor isoform can cause a sustained contraction of SM.[50] Thus, the relative expressions of these endothelin receptors are crucial for defining the SM tone including that of the CCSM. Although both ETA and ETB receptors exist in mammalian CCSM[51] including human;[42] current data support that ET-1-induced CCSM contraction appears to be mediated predominantly by ETA receptors.

Diabetes has been shown to upregulate ETB receptor expression in the STZ-induced type 1 diabetic rat stomach but to have no effect on ETA receptor expression.[52] In contrast, both ETA and ETB receptors are upregulated in type 2 diabetic rats.[44] Mixed results have been reported in the corpus cavernosum with one study demonstrating an upregulation of only the ETA isoform in response to type 1 diabetes[51] and another study finding only an upregulation of the ETB receptor.[54] Our work has revealed an increase in both the ETA and ETB receptors (at both the mRNA and protein levels) but with a more significant upregulation of the ETA receptor isoform in the alloxan-induced model of type 1 diabetes.[29] The same study also showed an increased expression of the ET-1 peptide (via immunohistochemical analysis) in the corpus cavernosum of diabetic rabbits, which correlated with functional changes, including increased sensitivity and maximum force production in response to ET-1 in the CCSM isolated from diabetic compared to normal animals.

Our studies have also suggested that the relevance of ET-1 to corporal smooth muscle physiology may depend on its ability to augment the contractile responses of other vasomodulators present in the human corpora. ET-1 potentiates contractile response of several spasmogens such as norepinephrine, serotonin, and angiotensin II in diverse vasculature and may affect corporal smooth muscle tone via augmentation of underlying α1-adrenergic activity.[53] Elevated ET-1 levels may reflect local overproduction of peptide from damaged endothelial cells with plasma spillover secondary to disease processes and cause an increased intracellular calcium level in diabetic cavernosal tissue.[54] Organic ED may thus be fostered through altered regulation of ET-induced vasoconstriction which leads to heightened CCSM tone. As ET-1 levels in serum are easily quantifiable, the potential exists for using ET-1 as a biomarker for ED. These data all suggest that ET-1 is a putative modulator of ED.

Nitric oxide (NO) induces vascular smooth muscle relaxation and is deemed by many to be the putative principal mediator of penile erection. Produced from L-arginine via nitric oxide synthase (NOS), NO is identified in corporal smooth muscle cells, and there is a consensus that endothelium-dependent relaxation in the corpora is achieved by activation of cholinergic receptors on corporal endothelial cells and increased NO production.[35,55,56] NO may be released via other mechanisms; for example, it may be related to mechanical deformation or shear-stress of the endothelial cells subsequent to the increased blood flow produced by helicine arteriole dilatation, or it may be released from nonadrenergic or noncholinergic neurons.[18] NO activates soluble guanylate cyclase which produces cGMP. Several families of phosphodiesterase enzymes are natural feedback inhibitors of that process. Cyclic GMP-specific phosphodiesterase 5 (PDE5) is such an enzyme and is present in the human corpora. Viagra™, Cialis™, and Levitra™ are potent and selective PDE5 inhibitors that revolutionized the field of oral agents in ED treatment. They function by inhibiting the breakdown of cGMP and thereby promoting smooth muscle relaxation. Moreover, advanced glycosylation end products, formed from glucose and amino groups of tissue proteins elevated in diabetic and/or aging patients, may contribute to diabetic ED by binding NO and thereby quenching its supply.[57] The collagen and elastin present in penile smooth muscle and tunica albuginea are suspected to be the target of injury by glycosylated end products formed in diabetic animals.[58,59] Deleterious effect on NO formation and diminished nitrergic innervation of the diabetic rat corpora has also been documented.[60–62] While NO mediates CCSM relaxation and penile erection, studies demonstrate significantly higher NOS activity in diabetic rats when compared with control rats, as well as a marked increase in plasma NO.[63] Despite the elevated NO levels, its action or pathway may be hindered in the diabetic corpora secondary to impaired receptors or transduction mechanism for second messengers, heightened tone of corporal smooth muscle cells, or increased catabolism.[63,64] Miller and associates demonstrate a reduction in the hydrolysis of cAMP and cGMP in diabetic rats and conclude that the increased intracellular cyclic nucleotide levels constitute an adaptive response to counteract the deleterious effects of diabetes.[65] The mechanism leading to the functional blockade of NO in diabetic penile tissues needs further elucidation.

Other investigators have corroborated the original conclusions of Ellenberg and Kolodny et al. that autonomic neuropathy is the primary cause of increased incidence of diabetic impotence.[7,8,22,66,67] ED may not be a late complication of diabetes and ED may be present early during the course of the disease. The diagnosis of ED may also lead to the discovery of otherwise unrecognized diabetes.[68] The correlation of bladder neuropathies or dysfunction in diabetic impotent patients, such as decreased bladder sensation, increased residual urine, and detrusor instability, is crucial in supporting autonomic neuropathy as a cause of diabetic impotence since the bladder and penis both receive autonomic innervation from the hypogastric sympathetic and the pelvic parasympathetic nerves. In our own lab, we have demonstrated detrusor overactivity in the streptozotocin-induced diabetic rat

model.[69] Ellenberg and Faerman both reported a high incidence of bladder dysfunction in diabetic impotent patients.[8,70] Neurophysiological, hormonal, and vascular investigations from Bermelmans and associates lead to a conclusion that diabetic urogenital neuropathy along with poor diabetes regulation plays a crucial role in the etiology of diabetic ED while vasculopathy appears to be of secondary importance.[71] Their studies demonstrate significantly lower glycosylated hemoglobin values and plasma glucose levels in potent diabetic men than in impotent ones, suggestive of better diabetic control in the former group. Morphologic abnormalities such as beaded thickenings, vacuolated thickenings, hyperargentophilia, and moniliform thickenings have been shown in the autonomic nerve fibers of diabetic corporal tissue,[70] but our earlier studies showed preserved sympathetic nerves retrieved from the corporal tissue of impotent diabetic men.[72] The host of neurotransmitters implicated in the physiology of penile erection, along with the various neuroeffector systems, also lend support to the notion that diabetic penile neuropathy is the primary origin of diabetic ED. Recently, Schaumburg et al. have shown in both ultrastructural and electrophysiological studies of the STZ-induced diabetic rat that there are morphologic changes of axonal dystrophy only after a prolonged period of hyperglycemia (>8 months).[73] This is in contrast to nerve conduction velocity in the unmyelinated fibers of the cavernous nerve, which is decreased as early as the second month after induction of diabetes. Reduction of intracavernous pressure with cavernous nerve stimulation is observed as early as 1 month after induction of diabetes in those same animals. These findings underscore the fact that gaps remain in our knowledge regarding the exact contribution of diabetic neuropathy to ED at the molecular and cellular levels. Is there a secondary response of the corporal tissue per se or changes in the myocytes when the innervation to the tissue is altered? Current efforts at the Urology Research Laboratory at the Albert Einstein College of Medicine focus on the differential control of smooth muscle cell tone in physiologically distinct tissues such as the bladder and corpora. Our findings in excitable bladder detrusor myocytes and non-excitable corporal smooth muscle indicate that differential organ function is attributable to quantifiable differences in the way that ionic mechanisms participate in the control of myocyte tone. Our data also support the hypothesis that altered neural and/or myocyte function will differentially contribute to diabetic ED and bladder dysfunction and can thus lead to novel therapeutic possibilities by better defining the mechanisms involving diabetic neuropathy or myopathy.

Integrative Corporal Smooth Muscle Physiology

Recent clinical data demonstrate the essential role of the CCSM in modulating penile blood flow during erection with an emerging consensus that the etiologic basis of organic ED lies in the primary changes of CCSM physiology and function.[74] Regardless of the primary defect or abnormality, CCSM relaxation is both necessary and sufficient to elicit an erection in many cases.[74]

The modulation of the CCSM tone is an intricate process necessitating the integration of a host of intracellular events and extracellular signals. Data reveal that the neurotransmitters that participate in erection and detumescence modulate CCSM tone largely via their effects on gap junctions as well as calcium and potassium channels.[74] Figure 26.1 depicts the major mechanisms regulating corporal smooth muscle tone. Broadly, events linked to calcium mobilization and muscle contraction increase the level of intercellular communication while events linked to the activation of cAMP and muscle relaxation decrease the level of intercellular communication.[10]

Potassium channels, ubiquitous in myocytes, appear to exhibit a greater diversity than any other ion channels. At least four distinct subtypes have been identified in the CCSM: calcium-sensitive potassium channel (Maxi-K or K_{Ca}), ATP-dependent potassium channel (K_{ATP}), inwardly rectifying channel (K_{ir}), and voltage-gated potassium channel (K_V). Of these four subtypes, the K_{ATP} and Maxi-K channels are the most thoroughly studied and are physiologically relevant to the control of CCSM tone. The importance of potassium channels to the modulation of CCSM tone is related to the intricate interplay between membrane potential, cellular excitability, and contractility.[75,76] In other words, sustained contractions of CCSM are dependent on continuous transmembrane calcium flux through voltage-dependent calcium channels, and hyperpolarization of CCSM cells via potassium

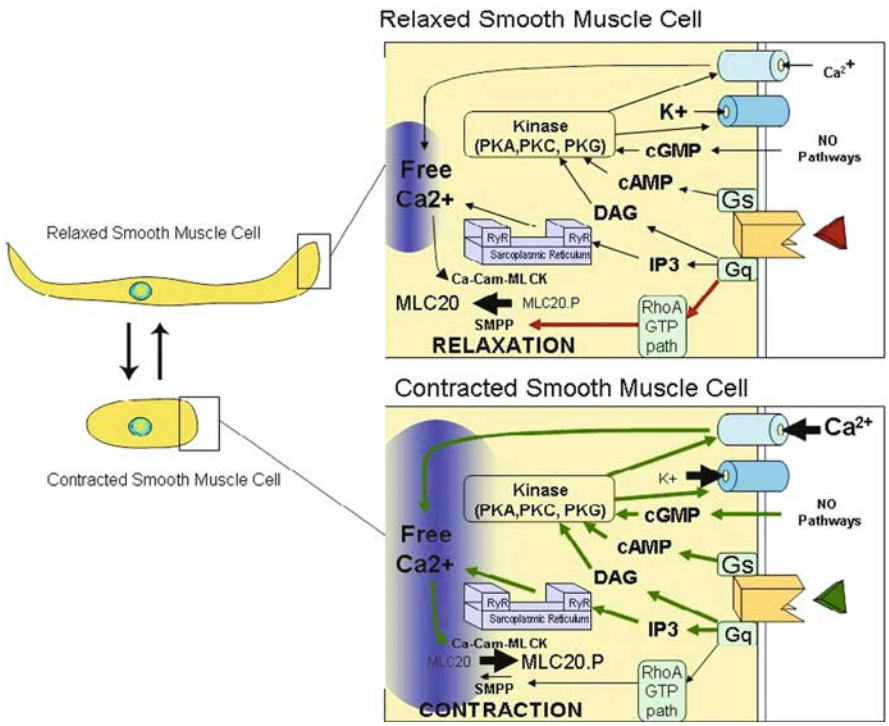

Fig. 26.1 This figure shows cellular enzymatic mechanisms needed to obtain smooth muscle cell relaxation (i.e., erection), as compared to smooth muscle cell contraction (i.e., penile flaccidity). Ca^{2+} = intracellular calcium ion concentration, PKA, PKC, PKG = protein kinases, NO = nitric oxide, MLCK = myosin light chain kinase, MLC = myosin light chain, cAMP = cyclic adenosinemonophosphate, cGMP = cyclic guanosinemonophosphate, DAG = diacylglycerol

channels may represent an important mechanism for modulating corporal muscle tone.[74] Recent studies report that diabetic corporal tissues from patients are less sensitive to relaxation with potassium modulators.

Gap junction proteins play a vital role in the initiation, maintenance, and modulation of CCSM tone.[77–79] The sparse neuronal innervation of CCSM may not explain their synchronized and coordinated relaxation, while the response of the CCSM to locally released or injected neuromodulators is rapid and diffuse. Our studies demonstrate the diffusion of current carrying ions and second messengers (calcium ions and IP_3) through gap junctions between coupled CCSM cells in culture.[77] A significant increase in connexin43 mRNA expression in the rat corpora is reported in STZ-induced diabetic rats,[80] and Giraldi et al. reveal a twofold to eightfold variability in connexin43 mRNA in corporal tissue isolated from patients with organic ED,[81] which signifies that the connexin43 mRNA level may be a crucial regulatory point in organic ED. Interestingly, changes in connexin43 mRNA expression are also correlated with physiologically significant alterations in other smooth muscle tissues such as the uterus.[82,83] Gap junction dysfunction may be accountable for the impaired smooth muscle relaxation and contraction coordination in vascular disease due to the presence of collagen fibers between cellular membranes.[84] Thus, there is strong evidence to support a role for intercellular communication in the integration of CCSM tissue responses, and gap junctions play an invaluable role in modulating CCSM tone and consequently penile erection.

Recently it has been shown that CCSM contraction can occur in the absence of changes in $[Ca^{2+}]$ by inhibiting SM myosin phosphatase (SMMP) activity. This process has been termed "calcium sensitization" of SM.[85] One such mechanism of "calcium sensitization" recently identified involves an enzyme known as Rho-kinase (ROK). ROK activity is regulated through a complex molecular pathway. One of the most important regulators of ROK activity is RhoA, a small GTP-binding protein.[86] ROK binds GTP-RhoA at its centrally located Rho-binding domain. This binding of RhoA causes ROK to migrate to the cell membrane where it is maximally active.[87] ROK

increases SM myosin phosphorylation (with no change in the intracellular calcium concentration) indirectly by inhibiting the phosphatase (SMMP) responsible for dephosphorylating SMM.[88] Our work has demonstrated a selective upregulation of the ROKβ isoform (compared to ROKα) in the corpus cavernosum of the diabetic rabbits.[29] Increased expression of ROK in an STZ type 1 model of diabetes was later reported by Bivalacqua et al. who also showed that transfection of a dominant negative form of ROK could improve ED.[89]

In contrast to activation by RhoA, Rho-kinase activity is inhibited by cGMP-dependent protein kinase-1 (PKG-1), which has been termed "calcium desensitization" as this reaction does not involve an alteration in the intracellular calcium levels. This decrease in "calcium sensitivity" results either indirectly via PKG-1 phosphorylation and inactivation RhoA (which prevents RhoA from activating ROK)[90,91] or directly via PKG-1 activation of SMMP.[92] The cGMP generated via nitric oxide-induced activation of guanylyl cyclase is considered the main mediator of CCSM relaxation, and preventing its degradation constitutes the mechanism of action of PDE5 inhibitors. The physiological relevance of PKG-1 in SM has been demonstrated by PKG-1 knockout mice. Of particular relevance to this review is that these mice cannot obtain normal erections.[93]

There are two PKG-I isoforms, PKG-Iα (76 kDa) and PKG-Iβ (78 kDa), which arise from the alternative splicing of a single gene[94,95] and differ in their amino-terminal autoinhibitory domains but are similar in their cGMP-binding sites and catalytic domains. Our laboratory has shown that the expression of PKG-1 (most significantly PKG-1α) is reduced in the CC in response to alloxan-induced diabetes in a type 1 diabetic rabbit model.[96] This study showed that the diabetes was associated with significantly decreased PKG-1 activity of CCSM in vitro, correlating with decreased CCSM relaxation. Immunofluorescence microscopy revealed a diabetes-associated decrease in PKG-1 in the CCSM cells. Bivalacqua et al. confirmed the upregulation of PKG-1 in response to diabetes in the STZ-rat and further showed that gene therapy with PKG-1α could restore PKG activity and erectile function in diabetic rats.[97]

Although once thought to merely serve structural roles in cell membranes, lipids are now known to participate in signal transduction pathways. One of the most rapidly emerging bioactive lipids is known as sphingosine-1-phosphate (S1P). This molecule, formed via the reversible phosphorylation of sphingosine and transported in the blood,[98] is emerging as a powerful player in the regulation of a number of important cellular processes including SM contractility and differentiation.[99] By acting on its three main mammalian S1P receptors (S1P1, S1P2, and S1P3), S1P has been shown to regulate a large number of diverse cellular pathways including the endothelin and Rho-kinase (ROK) contractile systems. In general, S1P has been shown to induce vasoconstriction at high doses (> 1 μM) while at lower doses of 10–100 nM, vasodilation has been observed.[100]

Preliminary experiments in our lab have demonstrated the expression of all three S1P receptor isoforms in the rat corpus cavernosum and have shown that S1P, at concentrations greater than 1 μM, cause contraction of rat CCSM. Using high-performance liquid chromatography (HPLC), our laboratory recently found that the serum level of S1P in male Zucker Diabetic Fatty (ZDF) rats (a genetic model of type 2 diabetes) is elevated threefold compared to lean age-matched control rats and correlates with a decrease in erectile function. Di Villa Bianca et al. have reported that human corpus cavernosum also expresses all S1P receptor isoforms and that at low concentrations, S1P activates eNOS and increases acetylcholine relaxation.[101] The relaxation would be presumed to be mediated by the S1P1 receptor, which has been associated with activation of eNOS, rather than the S1P2 and S1P3 receptors, which are more associated with contraction via the RhoA/Rho-kinase pathway.[100] These observations, coupled with the fact that S1P is present at high levels (0.2–4.0 μM) in normal serum, suggest the potential of using S1P serum levels as a biomarker for diabetes-induced ED.

Streptozotocin (STZ)–Induced Diabetic Erectile Dysfunction in a Rat Model

Our recent studies propose that differential organ function is attributable to quantifiable organ-specific differences in the way that ionic mechanisms participate in the control of myocyte tone. We hypothesize that altered neural functions (diabetic peripheral neuropathy), impaired myocyte function (loss or decrease in myocytes), or change in myocyte responsiveness to agonist stimulation (alterations in potassium channels or gap junctions) will differentially contribute to STZ-induced diabetic bladder and erectile dysfunction. These alterations may be

related to differences in the severity and duration of diabetes. Isolating the effects of altered myocyte function versus altered neural regulation in our experiments is monumental since a more direct or accurate cause-and-effect relationship can then be elucidated. Development of a more targeted remedy can thus be attempted. Diabetes or hyperglycemia may induce direct effects on myocyte function. It has been demonstrated that alterations in neural and myocyte function are unequivocally related to hyperglycemia and not to a nonspecific effect of STZ.[60,80] The following alterations have been observed in STZ-induced diabetic rats: a significant reduction in penile erectile reflexes, decreased erectile response to cavernous neurostimulation, loss of erectile rigidity similar to the loss of erection in diabetic men, and loss of efferent neurons as evidenced by altered synaptophysin staining.[60,61,102] In addition, preliminary studies in our lab have revealed that there is a diabetes-induced decrease in the number of neurofilaments within the corpora of STZ-induced diabetic rats compared to control rats. This change may be one of the early events in neuronal alteration that leads to ED. Diminished hyperpolarization of the CCSM, possibly secondary to decreased expression of functional potassium channels, may lead to impaired smooth muscle relaxation as hyperpolarization of CCSM cells via potassium channels may be vital in modulating CCSM tone.

Our studies reveal a significant diabetes-related difference in the maximal amplitude of the phenylephrine (PE, equipotent to endogenous norepinephrine on corporal tissue strips)-induced contractile response, and a virtually absent pinacidil-induced relaxation in the corporal tissue strips from STZ-diabetic rats. Moreover, our pharmacological assays that measure the ability of purinergic agonists (ATP and UTP) to induce changes in the intracellular calcium levels have shown a significant reduction in ATP-mediated calcium mobilization in the diabetic corporal tissue and a sevenfold decrease in the sensitivity of the corpora to ATP. This observation may reflect a functional reduction/expression of the P2-receptor, mediator of CCSM relaxation induced by stimulation of the penile purinergic innervation. These changes in purinergic signaling may possibly contribute to diabetic ED.

Through the aforementioned mechanism, STZ-induced alterations in potassium channel activity can manifest as quantifiable changes in their ability to modulate contractility. Based upon research in our lab, we have recently published on sialorphin and its human analogue opiorphin as markers for erectile dysfunction.[103,104] The genes encoding these proteins, Vcsa1 and hSMR3A, respectively, are significantly down-regulated in STZ-induced diabetic rats and humans with ED with or without diabetes. Injection of sialorphin itself directly into diabetic rat corpora was capable of increasing intracavernosal pressures. One possible explanation for this result is that sialorphin's presence is capable of inducing increased activity in the Maxi-K channel, which ultimately leads to relaxation of corporal smooth muscle. A separate study examined the effects of gene transfer of *Slo* (encoding the alpha subunit of Maxi-K) via naked plasma DNA into STZ-induced diabetic rats and how its injection appeared to restore erectile function in these diabetic rats.[105] Analysis in these rats revealed a durable response with increased levels of *Slo* transcript, Maxi-K, for over 4 weeks. This also correlated with increased time of longest erection as well as the intracavernosal pressure to systemic blood pressure ratio. There was also a fourfold increase in sialorphin levels compared to controls. Further work in this area revealed that Cialis™, a PDE5 inhibitor, given 2 h prior to erectile measurements, also increases sialorphin expression fourfold. This indicates that PDE5 inhibitors may rapidly induce the expression of sialorphin. With the combination of Cialis™ and *Slo*, there is a fivefold increase in sialorphin compared to the individual treatments. These positive results have led to human trials discussed later in this chapter.

Vascular Factors

Vascular abnormalities associated with diabetes mellitus and atherosclerosis constitute a major cause of organic ED. Atherosclerosis is the cause of approximately 40% of ED in men older than age 50, and is characterized by the proliferation of smooth muscle and the deposition of lipid or collagen in the vessel wall. The presence of arteriogenic ED in men older than age 50 is considered by some investigators as an ominous sign for the presence of atherosclerotic disease and microangiopathy in other parts of the body.[106,107] Diabetic retinopathy is often a manifestation of small vessel disease in diabetic patients. Diffuse vascular processes such as atherosclerosis can lead to arteriogenic ED by causing vessel obstruction or arterial insufficiency, commonly of the internal pudendal artery and sometimes of the collaterals, consequently reducing arterial inflow. Thickening of the capillary basement membrane and increased vascular permeability with extravasation of lipoproteins into the vessel walls

are considered to be the etiologies of small vessel disease in diabetic patients.[108] Jevtich and associates conclude from their studies that stenosis and obliteration of penile arteries is a primary contributor to diabetic ED.[109] Other studies demonstrate that in patients with leg ischemia, there is significant pudendal arterial stenosis in impotent diabetic and nondiabetic men compared to potent men.[109] Diabetes is also associated with an increased risk of developing hypercholesterolemia and hypercoagulopathy.[110] Hypercholesterolemia may contribute to ED by accelerating atherosclerosis;[107] thus, diabetic patients are subject to compounded risk factors and insults when they develop hypercholesterolemia and atherosclerosis independently. The hypercoagulopathic state, which is induced by increases in coagulation factors such as the von Willebrand factor and tissue plasminogen, is associated with diabetes and can lead to thrombosis and reduced arterial inflow.[111,112] Diabetic impotent patients may also have other vascular risk factors, such as hypertension and cigarette smoking, which can cause atherosclerotic vessel changes.[3,113–115] Corporal veno-occlusive dysfunction associated with atherosclerotic alterations is also implicated in the etiology of ED in diabetic men[116] via structural changes in the fibroelastic components of the corpora.

Diagnostic Modalities

What is the cause of the complaint?

The male sexual response is composed of five phases:

1. Libido
2. Erection
3. Orgasm
4. Ejaculation
5. Refractory period

As the first step in the evaluation process, a complete history and physical examination should be completed. It is imperative that the physician be cognizant of the presenting complaint. Patients may complain of being "impotent" when in reality they may have premature ejaculation, retrograde ejaculation, diminished libido, or a combination of symptoms. The work up and treatments are different for each. In the era of readily available oral agents and the constraints of office time posed by insurance companies and HMOs, it is imperative that the therapy be in harmony with the complaint.

The physical examination should be attentive toward sexual and genital development as well as identifying any vascular, endocrine, or neurologic abnormalities. Approximately 20% of men by history and physical examination alone will be overdiagnosed with organic ED.[117] Any patient who describes overt, rigid, and straight erections (for example, with mistress but not with wife or during masturbation) is likely to have a primary psychological cause of the problem. Referral for conjoint sex therapy is appropriate for such a complaint. A careful neurologic examination is important in a patient whose history is suggestive of peripheral or central neuropathies such as diabetes. The endocrine studies that may be performed for evaluation of impotent men are targeted toward the hypothalamic–pituitary–testicular axis. These assays measure serum testosterone, prolactin, thyroid, and luteinizing hormones. A screening glycosylated hemoglobin A1c or fasting blood sugar should also be obtained to assess for new onset ED as 13% of men with diabetes have ED as their first symptom.

To diagnose the presence of ED, initial tests such as Rigiscan™ analysis, visual sexual stimulation, and penile plethysmography (pulse volume recording) can be performed as baseline studies. Rigiscan™ analysis monitors nocturnal penile tumescence and rigidity by measuring penile circumference and radial rigidity through loops connected to a microcomputer that is strapped to the patient's thigh. Rigiscan™ remains the only objective way of monitoring the presence or absence of erectile ability. Intracavernous pharmacotesting can also serve as a treatment trial to assess the quality of erection. If erection is not achieved, the test should be considered as inconclusive and other diagnostic tests should be sought. Penile plethysmography is a good screening test that measures volume changes with each pulsatile expansion of the penis during flaccidity. Duplex sonography

is a minimally invasive initial diagnostic test of vascular impairment.[118,119] The advantages of penile duplex ultrasound include its abilities to visualize penile anatomy, to measure arterial flow velocity or peak systolic velocity, to assess arterial compliance and pharmacologic response, and to evaluate venous efflux.

Although autonomic neuropathy is the primary cause of erectile dysfunction, there is no direct method to assess the autonomic nervous system. Penile biothesiometry simply measures the sensory function or vibration perception threshold of the penis and can be used as an initial screening test. Aging and diabetes accelerate the diminished perception of vibratory sensation.[120] Since first described by Haldeman et al., somatosensory-evoked potential testing has evolved into a promising tool in the evaluation of neurogenically impotent patients.[121,122]

Although no tests can directly measure the autonomic component of erectile function, testing of the autonomic cardiovascular reflexes suggests that abnormal reflexes are associated with aging and organic impotence, indicating the equal importance of autonomic dysfunction in the etiology of erectile failure.[123] Cystometrography and tests of certain vascular functions regulated by the autonomic nervous system, including blood pressure and pulse response to cold, sympathetic skin responses to electrical stimulation, and orthostatic measurements of blood pressure and pulse, have been suggested as ways of identifying autonomic neuropathy in impotent patients.[124]

Therapeutic Options

After the diagnosis of ED is established, a treatment plan should be configured. The applicability of the particular therapeutic option is dependent on the underlying pathology, potential reversibility of the dysfunction, and the wishes of the patient.

No Treatment

Some 25–30% of patients are content to be told of the etiology of their dysfunction, and desire no further treatment.[120]

Medical Therapy

The drug therapies available to induce penile erection are nonspecific and may promote erection in the presence of psychological, hormonal, neurologic, or vascular pathologies. If there is a frank vascular obstruction or vessel stenosis, veno-occlusive dysfunction, corporal fibrosis, severe micro or macro angiopathy, drug treatment will be ineffective, and other noninvasive therapies must be sought.

The introductions of oral sildenafil (Viagra™), tadalafil (Cialis™), and vardenafil (Levitra™) have contributed to increased public awareness of ED. They exert their effect by prolonging the action of cGMP, thereby increasing calcium efflux and consequent corporal smooth muscle relaxation. Impotent patients with a long history of severe poorly controlled diabetes may not optimally benefit from PDE-5 inhibitors because of microangiopathy, altered myocyte function, and impaired neural regulation. Nonetheless Rendell et al. reported improved erections in 57% of diabetic impotent patients receiving sildenafil versus 10% in the placebo group, which is encouraging despite the pathophysiologic alteration diabetes can impose on penile physiology.[125] This study of 268 patients, however, excludes those presenting with more severe diabetic complications such as unstable glucose control and severe autonomic neuropathy. In other words, patients sustaining more severe diabetic complications may not be suited to administration of PDE5 inhibitors, despite the study's conclusion that oral sildenafil is an effective and well-tolerated treatment for men with diabetic ED. Price et al. also reported good efficacy of oral sildenafil in treating diabetic impotence, though only 21 men are included in the study and only 6 have evidence of autonomic neuropathy.[126] Guay has reported that control of diabetes made a difference in response to sildenafil. If the HbA1C was less than 9%, there was a 63% response rate. If the HbA1C was >9%,

the response rate dropped to 44%. [127] To reiterate, we believe that oral PDE-5 inhibitors may not be an effective treatment for impotent men suffering from more advanced or severe diabetes-induced pathophysiologic alterations. Nevertheless, the advent of a relatively effective oral agent for ED is encouraging, and since none of its adverse effects exacerbates diabetes, impotent patients with diabetes may be given a trial of an oral PDE5 inhibitor. Common minor side effects include headache, flushing, and blurred vision. The hypotensive effect of PDE-5 inhibitors in patients already receiving nitrates makes them absolutely contraindicated in these patients.

Patients with primary hormonal abnormalities such as severe hypotestosteronemia may benefit from testosterone therapy. Those with hyperprolactinemia induced by prolactin-secreting tumors can utilize oral bromocriptine, radiation, or surgical ablation of the pituitary tumor.

Prostaglandins have been identified in human corporal tissue and are known to modulate autonomic nerve function as well as the effects of vasoactive hormones that contribute to the myogenic tone of vascular smooth muscle.[128] Intraurethral alprostadil, the synthetic formation of prostaglandin E1, administered as a pellet in 500 μg quantities has rapid absorption rates and can induce penile erection in some patients. This "medicated urethral system for erection" or "MUSE" may incur side effects such as urethral pain and bleeding, hypotension, or infection.[129]

Intracorporeal injection of vasoactive agents is a minimally invasive therapy pioneered by Virag in 1983. The pharmacological erection can be induced with an intracavernous injection of 0.20 mL of Trimix (papaverine 30 mg/mL, phentolamine 5 mg, and prostaglandin E1, 25 μg, in 1.2 mL saline) or 10 μg of prostaglandin E1. Papaverine is a nonspecific phosphodiesterase inhibitor that prolongs the action of both intracellular cyclic AMP and cyclic GMP and causes vascular smooth muscle relaxation. This form of therapy works best in patients with good or marginal penile blood supply and properly functioning CCSM and may be used alone or in conjunction with other drugs.

Lastly, the results of the successful transfer of the Maxi-K gene in both the aging and the diabetic rat models that results in normalization of erectile function has led to the first human trial of hMaxi-Kgene transfer in males with ED.[130] In a recently completed phase I trial that enrolled 11 patients, the safety and tolerability of escalating hMaxi-K doses were assessed. No adverse effects were noted. Secondary efficacy objectives were measured primarily by use of the International Index of Erectile Function (IIEF) scale. In two of the patients that were given the two highest doses of 5000 and 7500 μg of the product, clinically significant responses were noted and maintained through the 24-week study period. The successful phase I trial is leading to further work in clinical trials to study the efficacy of this gene therapy.

Vacuum Devices

The external vacuum device offers a relatively safe and nonsurgical alternative for almost all types of ED. When placed over the penis it generates a vacuum, which pulls blood into the corpora creates an erection-like state. A tourniquet or tension band is then placed at the penile base in order to trap blood in the shaft, and the band is left in place for a maximum of 30 min.

Surgical Treatment

Penile prosthesis is an effective surgical alternative for impotent patients with organic or systemic diseases. Either a semi-rigid or inflatable prostheses can be inserted. The primary side effect is infection at the time of surgery, with a reported incidence of about 3%.[131] Studies report that penile prosthesis is effective in diabetic impotent men with low-complication rates.[132,133]

Future Directions in Diabetic Erectile Dysfunction

ED is commonly associated with diabetes, and each disease process by itself incurs debilitating consequences. Diabetes is now the leading cause of new blindness in adults, end-stage renal disease, and lower-extremity amputations not related to injury. It is one of the major contributing factors to cardiac disease and stroke, as

well as a host of other comorbidities. The diabetes-related changes observed in ED and bladder function are permanent and require medical therapy to ameliorate the symptoms.[134] Since hyperglycemia is responsible for complications and glucose management remains problematic, development of diagnostic biomarkers and novel therapeutic options continue to be a high priority. There is an impressive reduction in the incidence and progression of microangiopathy and neuropathy with tight glycemic control. Even with rigorous control, however, complications develop. Since the pathophysiology of diabetes is related to the duration and severity of hyperglycemia and its complications,[135] aggressive tight metabolic control from the onset of disease is essential and prevention of diabetes mellitus is key to avoiding ED.

Summary

Recognized since antiquity, diabetes mellitus has become ubiquitous in many developing and newly industrialized countries. Dubbed the silent killer, diabetes causes more deaths per year in the United States than AIDS. Although the effect of diabetes on sexual function in men has been recognized for the last 200 years, the association has been well understood only during the last three decades. The impact of diabetes on male sexual function is emphasized by the fact that more than 50% of patients with diabetes have ED. The most common causes of diabetic ED include autonomic neuropathy and vascular abnormalities often associated with diabetes. Numerous neurotransmitters are implicated in the modulation of penile erection, including vasoactive intestinal polypeptide, endothelin-1, and nitric oxide, strengthening the notion that diabetic neuropathy plays a role in the genesis of diabetic ED. Our current research focuses on the gap junctions and potassium channels at the molecular level. We are working toward deciphering the mechanisms governing penile smooth muscle relaxation and contraction to help guide novel therapeutic options.

Several therapeutic options are offered for ED: medical therapy such as oral PDE-5 inhibitors, intracorporeal pharmacotherapy, vacuum devices, or surgical modalities such as penile prosthesis. The frontier of medical management will undoubtedly include gene therapy as indicated by the positive results in phase I trials of Maxi-K. Despite the advancement and efficacy of such treatments, the biggest hope of patients and physicians alike will be a cure for diabetes and thus the eradication of its associated comorbidities such as ED. As we strive to search for more answers, a cure for diabetes mellitus may be on the horizon.

Acknowledgments We would like to thank Sarah Collins, M.D., Urogynecology Fellow at the Albert Einstein College of Medicine, for making valuable contributions in editing the text.

We also want to thank Kelvin Davies, Ph.D., Associate Professor in the Department of Urology at Albert Einstein College of Medicine, for his diagrammatic representation of smooth muscle physiology.

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