Male Sexual Dysfunction in Diabetes Mellitus

28

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Abstract

Erectile dysfunction (ED), also known as impotence, is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual function. Based on these data and the US population projection for the year 2020 of more than 74 million men 45–84 years old, ED will affect more than 38 million men and millions more over the age of 84. Diabetic men have a more than threefold increase in risk of ED compared to their nondiabetic counterparts. Diabetes mellitus (DM) is a common chronic disease affecting 285 million people and is expected to increase to 7.7% by 2030. Because both ED and DM are so prevalent, it is not surprising the two are associated. ED is reported to occur in more than 50% of men with diabetes. The penis is a complex vascular organ that requires the coordination of an initiated spinal reflex to a vascular process in which nerves, sinusoidal and vascular endothelium, and smooth muscle (SM) cells are involved to achieve satisfactory penile erection. In men with DM who have impaired erection, there is the inability to either obtain or maintain a state of penile rigidity sufficient for satisfactory intercourse. In those having DM with ED, there is a panoply of possible adverse effects on the neurological function, vascular (including smooth muscle and endothelium) supply, cell membranes, contractile proteins, and a myriad of neurotransmitters and second messengers that can interfere with the normal mechanism of erection. These potential mechanisms and modern therapies for ED are reviewed as a starting point for understanding the basis of this important physiological function.

Keywords

Erectile dysfunction • Endothelial • Corpora cavernosal smooth muscle • Contractile proteins • Ion channels • Maxi-k channel • Contractile proteins • Diabetes mellitus

Contents

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Introduction

Male sexual dysfunction can be classified according to the following categories: erectile dysfunction (ED), orgasmic, ejaculatory dysfunction, decreased libido, and refractory period dysfunction. Of these several disorders, two, ED and ejaculatory dysfunction, are most often seen in men with diabetes mellitus (DM). Therapy for the ED component 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 the last two decades, since the introduction of Viagra™, there has been an escalating public awareness of the magnitude of ED, mainly attributable to the marketing of Viagra™, Levitra™, and Cialis™. 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 [2]. Based on these data and the US population projection for the year 2020 of more than 74 million men 45–84 years old, ED will affect more than 38 million men and millions more over the age of 84 [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. DM is a common chronic disease affecting 285 million people, corresponding to 6.4% of the world's adult population in 2010 and expected to increase to 7.7% by 2030 [5]. Because both ED and DM are so prevalent, it is not surprising the two are associated. ED is reported to occur in more than 50% of men with diabetes [6]. Conversely, the prevalence of DM in a population of men with ED was recently reported by Mazilli et al. as being 19.5% [7]. After aging, DM is the single most common cause of ED. In men with diabetes, the ED occurs at an earlier age and the prevalence increases with disease duration [8, 9]. It is estimated that 50% of the ten million men with DM have ED with both type 1 diabetes (T1D) and type 2 diabetes (T2D) nearly equally associated with ED. The prevalence of ED increases with age for both groups, and after taking age into account, studies have shown that the T2D men have a lower rate of ED than T1D men [10].

Etiology

ED is multifactorial in origin but can be classified as organic, psychogenic, or a mixture of each [11]. Organic ED can be secondary to vasculogenic, neurogenic, hormonal, or corpus cavernosum smooth muscle (CCSM) 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 DM are autonomic neuropathy, vascular abnormalities, endothelial changes, and alteration of the CCSM. Vascular abnormalities are often associated with DM, reflecting disease in major arteries resulting in arterial insufficiency, veno-occlusive dysfunction, and microvascular abnormalities [11–19]. CCSM abnormalities, such as enhanced CCSM tone, are also essential factors in DM-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

Table 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
Endocrine	Brucellosis
Hyperthyroidism	Tuberculosis
Hypothyroidism	AIDS
Hypogonadism	Trypanosomiasis

medications, are commonly associated with ED [11–19]. Cummings et al. describe the striking degree of overlap between the risk factors of ED and common comorbidities of DM: cardiovascular disease, treated and untreated hypertension, multiple drug therapy, neuropathy, and obesity [16]. Thus the vulnerability of diabetic men to ED is further compounded by their additional need for multiple medications for other DM-associated medical conditions. Finally, trauma, irradiation, or pelvic surgery can also result in iatrogenic ED. Table 1 summarizes the various processes that contribute to ED.

General Penile Erection Physiology

The presentation of diabetic ED can be described in one of three ways: (1) asymptomatic DM followed years later by impotence, (2) impotence as a first sign of DM, and (3) temporary impotence resulting from poorly controlled DM, which is more likely caused by associated malnutrition and weakness [19]. 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 erectile portion of the penis is composed of separate, paired structures, the crura, which are attached by dense fascia 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 erectile bodies to function as a single unit. The corora contain a meshwork of interconnected cavernosal spaces known as the 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 SM cells [20]. The arterial inflow to the penis is the end terminal of the internal pudendal artery, a branch of the hypogastric (aka 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 within the cavernosal bodies), and dorsal (above the cavernosa) penile end arteries. The cavernosal arteries give off multiple helicine branches that are tortuous and contracted in the flaccid state and become straight and larger in caliber during erection. The blood from the helicine arteries fills and expands the lacunar space thus enlarging and lengthening the penis. It is the rise of intracavernosal pressure (ICP) in relation to mean systolic levels that ultimately determines erectile function.

The penis is a complex vascular organ that requires the coordination of an initiated spinal reflex to a vascular process in which nerves, sinusoidal and vascular endothelium, and SM cells are involved to achieve satisfactory penile erection [21]. Any abnormality that affects the integrity of the penile vasculature may result in ED. Four physiologic mechanisms are necessary to effect penile erections: (1) neural innervation, (2) 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. The CCSM tone is thus a primary determinant of erectile function. In the flaccid state, the cavernosal arteries and CCSM 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 ICP increases without any accompanying increase in systemic pressure. Relaxation of the trabecular SM causes increased compliance of the cavernosal spaces, leading to penile engorgement and erection. In the fully erect state, compression of the trabecular SM 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. Thus an erect penis cannot be decompressed with external pressure during erection. Malfunction of this veno-occlusive mechanism secondary to reduced blood flow, a venous outflow abnormality, incomplete relaxation of the SM, or malfunction of the collagen fibers results in ED. Detumescence ensues during contraction of the trabecular SM, with reduction of arterial blood flow to the prestimulation level and reopening of venous outflow channels. The ICP declines leading to the flaccid state. Any interruption or interference in this cascade of vascular events may precipitate ED [22–24].

Pathophysiology of Erectile Dysfunction and Diabetes Mellitus

Neurological/Biochemical Physiology

The Physiological Problem

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

Neurological Changes

There is a long-standing view that ED in men with DM is primarily caused by neurological abnormalities [22–25]. Ellenberg attributed the increased incidence of diabetic impotence to autonomic neuropathy [12, 13]. 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 neurotransmitter releasing RhoA/Rho-kinase system) and those that mediate relaxation (acetylcholine, nitric oxide, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide, adrenomedullin, adenosine triphosphate (ATP), adenosine, and the prostanoids) [21]. 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 [26]. Moreover, in vitro experiments on human erectile tissue treated with exogenous acetylcholine have demonstrated contraction or relaxation, or no responses at all. Saenz de

Tejada et al. suggest that acetylcholine is probably an inhibitory modulator of adrenergic constrictor nerves and a facilitatory modulator of nonadrenergic noncholinergic relaxation [27]. 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 [28].

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 [29]. Animal experiments show that the sympathetic noradrenergic fibers innervating the penis appear to demonstrate neuropathic changes and markedly reduced norepinephrine content in streptozotocin (STZ)-induced diabetic rats with hypoglycemia supporting the finding in human studies that noradrenergic sympathetic nerve damage in the penis is a complication of DM [30–33]. 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 [34]. However, in an animal model of T1D, we found that there was no significant alteration in the amount of force produced in response to phenylephrine compared to controls [35].

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 VIP. A potent vasodilator contained in the neurons of the major pelvic ganglion, VIP-immunospecific fibers have been demonstrated in cavernosal tissue [36]. Experiments have demonstrated a dose-dependent relaxation response to VIP [37], and VIPergic nerves have been found to be depleted in the corpora of diabetic men [38]. Additional data demonstrate a consistent reduction of VIP-like immunoreactivity density in penile disease from STZ-diabetic rats and human diabetic penile tissue when compared with control subjects [39]. 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 DM [40].

Endothelial Effects

Endothelial cell-derived modulators, such as endothelin-1 (a potent vasoconstrictor peptide), nitric oxide, and prostanoids, have been identified in the corpus cavernosum [41, 42]. 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, each the product of a separate gene and differing from one another by only a few amino acids [43, 44]. 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 [45]. ET-1, the most well characterized and predominant ET in normal plasma, is synthesized by endothelial cells [44], including corpus cavernosal endothelial cells and CCSM cells [46]. 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 [47].

Endothelin levels in plasma are elevated in the diabetic state in experimental animal models of both T1D [48] and T2D [49]. ET-1 levels are also elevated in diabetic humans as shown in a recent study by Shestakova et al. that revealed a significant increase in plasma endothelin levels in T1D patients. The level of endothelin in the plasma correlated positively with the severity of renal disease in patients with T1D [50]. Migdalis et al. reported elevated endothelin levels in T2D patients [51]. 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 [52].

The two main subtypes of ET receptors are referred to as ETA and ETB and are encoded by separate genes [53, 54]. Activation of one ETB receptor isoform has been shown to cause a transient vasodilation while activation of either the ETA or the alternatively spliced ETB receptor isoform can cause a sustained contraction of SM. 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 including human [47], current data support that ET-1-induced CCSM contraction appears to be mediated predominantly by ETA receptors [55]. DM has been shown to upregulate ETB receptor expression in the STZ-induced T1D rat stomach but to have no effect on ETA receptor expression [56]. In contrast, both ETA and ETB receptors are upregulated in type 2 diabetic rat heart [49]. 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 DM [55] and another study finding only an upregulation of the ETB receptor [57]. 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 T1D [35]. 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 SM physiology may depend on its ability to augment the contractile responses of other vasomodulators present in the human corpora. ET-1 potentiates contractile responses of several spasmogens such as norepinephrine, serotonin, and angiotensin II in diverse vasculature and may affect CCSM tone via augmentation of underlying α1-adrenergic activity [47]. 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 [57]. 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 SM 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 CCSM 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 [58, 59]. 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 [25]. NO activates soluble guanylate cyclase which produces cyclic GMP (cGMP). Several families of phosphodiesterase enzymes (PDEs) are natural feedback inhibitors of that process. cGMP-specific phosphodiesterase 5 (PDE5) is such an enzyme and is present in the human corpora. Phosphorylation of PDE5 and binding of cGMP to its noncatalytic sites mediate negative feedback regulation of the cGMP pathway [60]. 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 SM relaxation. Moreover, advanced glycosylation end products (AGE 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 [61]. The collagen and elastin present in penile SM and tunica albuginea are suspected to be the target of injury by AGE products formed in diabetic animals. Deleterious effects on NO formation and diminished nitrergic innervation of the diabetic rat corpora has also been documented [62–64]. 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 [65]. 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 SM cells, or increased catabolism [65, 66]. Miller and associates demonstrate a reduction in the hydrolysis of cyclic AMP (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 DM [67]. Angulo et al. reported that DM exacerbates the functional deficiency of the NO/cGMP pathway associated with ED in human corpus cavernosum and penile arteries suggesting that this deficiency could be responsible for ED in diabetic men and would explain their reduced response to treatment [68]. The mechanism leading to the functional blockade of NO in diabetic penile tissues needs further elucidation.

Unlike neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS) that have a defined role in the molecular mechanism of erection, inducible nitric oxide synthase (iNOS) has been proposed to counter the aging or injury-associated fibrosis in the penile corpora. Related to diabetes, Ferrini et al. reported that the genetic inactivation of inducible nitric oxide synthase (iNOS) intensifies fibrosis and oxidative stress in the penile corpora cavernosa in STZ-induced T1D mice [69]. Supporting this data is a study by Wang et al. that utilized novel promoter targeted saRNAs and demonstrated that saRNA-mediated iNOS overexpression in the penis can restore erectile function in STZ-induced diabetic rats via the nitric oxide-cyclic guanosine monophosphate pathway [70].

In T2D men, Mandosi et al. demonstrated that after 3 months, the PDE5 inhibitor sildenafil reduced the endothelial function marker P-selectin expression on monocytes and also exerted a beneficial effect on glycometabolic control [71]. Also, in a high-fat-diet-induced model of T2D ED, Ellati et al. showed that PDE5 levels were increased and cGMP levels were decreased, but in contrast, mice with T1D did not have increases in PDE5 [72]. Angiopoietin-1 (Ang1), the ligand of the Tie2 receptor tyrosine kinase, is an angiogenic growth factor that specifically functions to generate a nonleaky, stable, and functional vasculature. Jin et al. demonstrated that intracavernous delivery of synthetic Ang1 increased the expression of phosphor-eNOS, cGMP, and cAMP and restored endothelial cell arrangement that resulted in physiologically relevant restoration of erectile function in both T1D and type T2D mouse models [73].

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 [12, 13, 27, 74, 75]. ED may not only be a late complication of DM but also may be present early during the course of the disease. The diagnosis of ED may lead to the discovery of otherwise unrecognized DM [76]. 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 STZ-induced T1D rat model. Bladder dysfunction has been reported in diabetic impotent patients [77]. Neurophysiological, hormonal, and vascular investigations from Bermelmans and associates lead to a conclusion that diabetic urogenital neuropathy along with poor DM regulation plays a crucial role in the etiology of diabetic ED while vasculopathy appears to be of secondary importance [79]. 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, and hyperargentophilia have been shown in the autonomic nerve fibers of diabetic corporal tissue [77], but our earlier studies showed preserved sympathetic nerves retrieved from the corporal tissue of impotent diabetic men [32].

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 [79]. 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) [80]. 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 DM. Reduction of ICP with cavernous nerve stimulation is observed as early as 1 month after induction of DM in the same animals [81]. 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.

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 [82]. Regardless of the primary defect or abnormality, CCSM relaxation is both necessary and sufficient to elicit an erection in many cases [83].

At the basis of the molecular mechanism for erectile function is the interaction of SM myosin and alpha-actin. Zhang et al. reported a novel STZ-induced diabetes-specific effect on alternative splicing of the SM myosin heavy chain and essential light chain genes to a SM myosin isoform composition favoring a heightened contractility and ED. A switch to a more contractile phenotype was supported further by total SM myosin expression increase [84]. In a similar STZ type 1 DM model, Wei et al. showed a decrease in the expressions of the SM phenotype associated proteins α-SM actin, calponin, SM myosin heavy chain, smoothelin, and myocardin and a switch to a less contractile state of the myocytes [85]. He et al. showed that gene transfer of myocardin to the penis of STZ-induced diabetic rats restored expressions of SM pheotypic markers and in vivo erectile function [86].

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 [87–91]. Figure 1 depicts the major mechanisms regulating corporal SM 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 [82, 87–91].

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 (KV). Of these four subtypes, the KATP 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 [87, 88]. 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 channels may represent an important mechanism for modulating corporal muscle tone

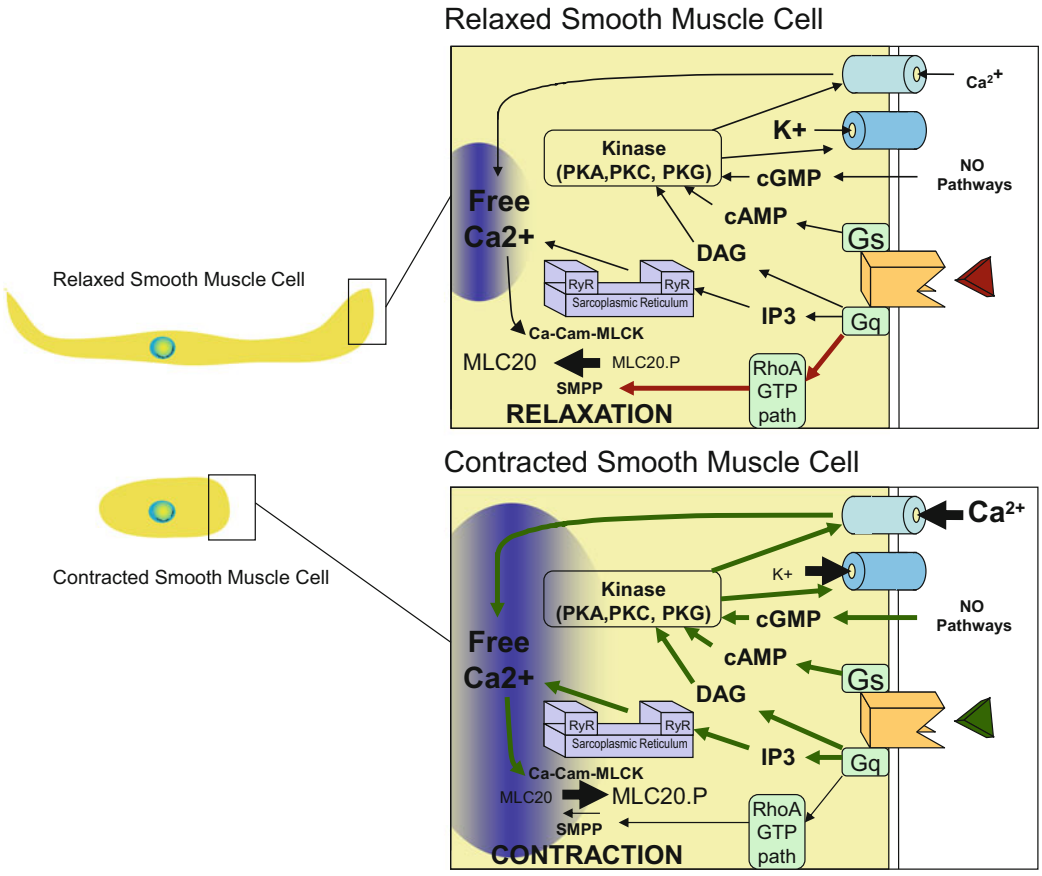

Fig. 1 This figure shows cellular enzymatic mechanisms needed to obtain smooth muscle cell relaxation (i.e., erection), as compared to smooth muscle cell contraction (i.e., penile flaccidity). Ca^{2+} intracellular calcium ion concentration, *PKA*, *PKC*, *PKG* protein kinases, *NO* nitric oxide, *MLCK* myosin light chain kinase, *MLC* myosin light chain, *cAMP* cyclic adenosinemonophosphate, *cGMP* cyclic guanosinemonophosphate, *DAG* diacylglycerol

[83]. Recent studies report that diabetic corporal tissues from patients are less sensitive to relaxation with potassium modulators. Zhu et al. showed that STZ-induced DM can significantly reduce erectile function in rats, which may be related to the significantly decreased expression of SK3 (one of the small conductance calcium-activated potassium channels) in the corpus cavernosum [92].

Gap junction proteins play a vital role in the initiation, maintenance, and modulation of CCSM tone [89–91]. 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 [90]. A significant increase in connexin43 mRNA expression in the rat corpora is reported in STZ-induced diabetic rats [93], and Giraldi et al. reveal a twofold to eightfold variability in connexin43 mRNA in corporal tissue isolated from patients with organic ED [94], 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 SM tissues such as the uterus [95, 96]. Gap junction dysfunction may be accountable for the impaired SM

relaxation and contraction coordination in vascular disease due to the presence of collagen fibers between cellular membranes. Thus, there is strong evidence to support a role for intercellular communication in the integration of CCSM tissue responses and that gap junctions play an invaluable role in modulating CCSM tone and consequently penile erection.

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 [97]. 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 [98]. 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 [99]. ROK increases SM myosin phosphorylation (with no change in the intracellular calcium concentration) indirectly by inhibiting the phosphatase (SMMP) responsible for dephosphorylating SMM [100]. Our work has demonstrated a selective upregulation of the ROKβ isoform (compared to ROKα) in the corpus cavernosum of the alloxan-induced diabetic rabbits [35]. Increased expression of ROK in an STZ type 1 model of DM was later reported by Bivalacqua et al. who also showed that transfection of a dominant negative form of ROK could improve ED [101].

Chronic treatment with Angiotensin-(1–7) reversed abnormal reactivity in the corpus cavernosum and normalized diabetes-induced changes in the protein levels of, among other enzymes, ROKα and ROKβ in a rat model of type T1D [102]. In prediabetic obese Zucker rats (OZRs), ROKα expression was augmented and the Rho-kinase inhibitor Y-27632 inhibited phenylephrine and KCl-induced CCSM contraction to a greater extent in the OZRs [103]. Li et al. reported that chronic treatment with an oral rho-kinase inhibitor (fasudil) restored erectile function by suppressing corporal apoptosis in diabetic rats [104]. 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) [105] or directly via PKG-1 activation of SMMP mediated by cGMP-dependent protein kinase Iα (cGKIα) [106]. The cGMP generated via NO-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 in PKG-1 knockout mice. Of particular relevance to this review is that these mice cannot obtain normal erections [107].

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 [107–109] 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 DM in a type 1 diabetic rabbit model [110]. This study showed that the DM was associated with significantly decreased PKG-1 activity of CCSM in vitro, correlating with decreased CCSM relaxation. Immunofluorescence microscopy revealed a DM-associated decrease in PKG-1 in the CCSM cells. Bivalacqua et al. confirmed the downregulation of PKG-1 in response to DM in the STZ-rat and further showed that gene therapy with PKG-1α could restore PKG activity and erectile function in diabetic rats [111].

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 [112], is emerging as a powerful player in the regulation of a number of important cellular processes including SM contractility and differentiation [113]. By acting on its three main mammalian 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 [114].

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 found that the serum level of S1P in male Zucker Diabetic Fatty (ZDF) rats (a genetic model of type 2 DM) is elevated threefold compared to lean age-matched control rats and correlates with a decrease in erectile function (unpublished data). 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 of CCSM [115]. 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 closely associated with contraction via the RhoA/Rho-kinase pathway [114]. 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 DM-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 function (diabetic peripheral neuropathy), impaired myocyte function (loss or decrease in myocytes), or change in myocyte responsiveness to agonist stimulation (alterations in potassium channels, gap junctions, or other SM regulatory proteins) will differentially contribute to STZ-induced diabetic bladder and ED. These alterations may be related to differences in the severity and duration of DM. 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. DM 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 [62, 116]. 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 diminished synaptophysin staining [62, 63]. In addition, preliminary studies in our laboratory have revealed that there is a DM-induced decrease in the number of neurofilaments within the corpora of STZ-induced diabetic rats compared to control rats [80]. 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 SM relaxation as hyperpolarization of CCSM cells via potassium channels may be vital in modulating CCSM tone.

Our studies reveal a significant DM-related difference in the maximal amplitude of the contractile response induced by phenylephrine (PE, equipotent to endogenous norepinephrine on corporal tissue strips) 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 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 laboratory, we have published on sialorphin and its human analogue opiorphin as markers for ED [117, 118]. The genes encoding these proteins, Vcsa1 and hSMR3A, respectively, are significantly downregulated in aged rats (unpublished) and humans with ED with or without DM [119].Injection of sialorphin itself directly into aged rat corpora was capable of increasing ICP [117]. 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 SM. 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 [120]. 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 ICP 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. (unpublished) These positive results have led to human trials discussed later in this chapter.

Vascular Factors

Vascular abnormalities associated with DM 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 SM 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 the coronary arteries and other parts of the body [121–123].

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. Jevtich and associates conclude from their studies that stenosis and obliteration of penile arteries is a primary contributor to diabetic ED [124]. 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 [125]. DM is also associated with an increased risk of developing hypercholesterolemia and hypercoagulopathy [126]. Hypercholesterolemia may contribute to ED by accelerating atherosclerosis; [125] 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 DM and can lead to thrombosis and reduced arterial inflow [127, 128]. Impotent diabetic patients may also have other vascular risk factors, such as hypertension and cigarette smoking, which can cause atherosclerotic vessel changes [128]. Corporal veno-occlusive dysfunction associated with atherosclerotic alterations is also implicated in the etiology of ED in diabetic men via structural changes in the fibroelastic properties, i.e., an increase in stiffness because of fibrosis and smooth muscle loss in the arterials [129–133].

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 comprehensive history and physical examination should be completed. It is imperative that the physician be cognizant of the presenting complaint. This is particularly important in the present setting of high patient volume throughput and electronic questionnaires. 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 true problem and not the initial 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 or permanent ED [134]. 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. The age of the patient is a significant factor. Young men without risk factors of DM or hypertension are more likely to have a reversible psychological problem. Referral for conjoint sex therapy is appropriate for such a complaint. However, many men are resistant to such a recommendation. In the era of PDE5 therapy, a short course of one of the available drugs frequently elicits a positive response. A careful neurologic examination is important in a patient whose history is suggestive of peripheral or central neuropathies such as DM. 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 plasma glucose should also be obtained to assess for new onset ED as 13% of men with DM 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. The Rigiscan™, for many years the hallmark of objective testing, is no longer supported by the manufacturer and is sadly unavailable for use. Duplex sonography is a minimally invasive initial diagnostic test of vascular impairment [136, 137]. 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 [135, 136].

Although autonomic neuropathy is the primary cause of ED, there is no direct method to assess the autonomic nervous system. Semmes-Weinstein monofilaments and biothesiometry measure the sensory function or vibration perception threshold of the penis and can be easily used as an initial screening test. Aging and DM accelerate the diminished perception of and superficial vibratory sensation [137–139]. 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 [140]. Testing modalities that are rarely used but are available include 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. All of these

have been suggested as ways of identifying autonomic neuropathy in impotent patients.

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 [138].

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 significant vascular obstruction veno-occlusive dysfunction, corporal fibrosis, or severe micro- or macro-angiopathy, drug treatment will be ineffective and other noninvasive therapies must be used.

The introduction of oral sildenafil (Viagra^{TM}), tadalafil (Cialis^{TM}), and vardenafil (Levitra^{TM}) (may be better to give scientific names upon first usage earlier on in manuscript) have contributed to increased public awareness of ED. These agents exert their effect by prolonging the action of cGMP, thereby increasing calcium efflux and consequent CCSM relaxation. Impotent patients with a long history of severe poorly controlled DM may not optimally benefit from PDE5 inhibitors because of microangiopathy, altered myocyte function, and impaired neural regulation. Nonetheless Rendell et al. reported improved erections in 56% of diabetic impotent patients receiving sildenafil versus 10% in the placebo group, which is encouraging despite the pathophysiologic alteration DM can impose on penile physiology [141]. 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 [142]. Guay has reported that control of DM 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% [143]. To reiterate, oral PDE5 inhibitors may not be an effective treatment for impotent men suffering from more advanced or severe DM-induced pathophysiologic alterations. Nevertheless, the advent of relatively effective oral agents for ED is encouraging, and since none of their adverse effects exacerbates DM, impotent patients with DM may be given a trial of an oral PDE5 inhibitor. Common minor side effects include headache, flushing, and blurred vision. The hypotensive effect of PDE5 inhibitors in patients already receiving nitrates makes them absolutely contraindicated in these patients.

Recent attention has focused on combinational therapy with PDE5 inhibitors. For example, Choi et al. reported in a rat study that chronic administration of PDE5 or glycemic control with insulin resulted in restoration of overt DM-induced ED but that the combination of both treatments was superior to monotherapy with insulin or PDE5 [144]. It was also reported that nebivolol (a selective β1-blocker) potentiates the efficacy of PDE5 inhibitors to relax CCSM and penile arteries from diabetic patients by enhancing the NO/cGMP pathway [145]. Another combinational study showed that Ca^{2+}-activated K^{+} channel (KCa) stimulation recovers the reduced efficacy of PDE5 inhibition in diabetic ED suggesting a therapeutic potential for KCa activation in diabetic ED [146]. Fukuhara et al. determined that treatment with either resveratrol or vardenafil elevated cGMP level in CCSM

cells and improved erectile function in STZ-induced diabetic rats and that furthermore, a synergistic effect of these two compounds was observed both in vitro and in vivo [147].

A role for testosterone in modulating the efficacy of PDE5 inhibitors has also been proposed. Testosterone undecanoate restored erectile function in a subset of patients with venous leakage in a series of case reports [148]. Also, supporting this hypothesis is a study by Zhang et al. that found testosterone restores DM-induced ED and sildenafil responsiveness in two distinct animal models of chemical diabetes (T1D in rabbits and T2D in rats) [149]. Mostafa et al. further showed that frequent low-dose use of sildenafil and/or tadalafil combined with testosterone had a pronounced antiapoptotic effect on the cavernous tissues of aged diabetic rats [150].

Patients with primary hormonal abnormalities such as severe hypotestosteronemia may benefit from testosterone therapy. Those with hyperprolactinemia induced by prolactin-secreting tumors (prolactin levels greater than 100–200 μg/L) can be treated with oral bromocriptine or dopamine – agonists for chemical shrinkage of the tumor as first line therapy [151].

Prostanoids are synthesized in human corporal tissue and can be metabolized locally. Their role in human erection is unclear as is the effect of diabetes on them [152]. Intraurethral alprostadil, the synthetic form 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. Intracorporal injection of vasoactive agents is a minimally invasive therapy initiated in 1983. The pharmacological erection can be induced with an intracavernous injection of vasodilating agents such as papaverine, phentolamine, and prostaglandin E1, alone or in combination. Papaverine is a nonspecific phosphodiesterase inhibitor that prolongs the action of both intracellular cyclic AMP and cyclic GMP and causes vascular SM 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.

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 creating 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. These devices are used predominately by older men in long standing relationships. The "mechanical" process is a significant negative to many potential users.

Surgical Treatment

Penile prosthesis is an effective surgical alternative for impotent patients. The prostheses have been used since the late 1960s and early 1970s. Either a semi-rigid or inflatable prostheses can be inserted. Through the years there have been modest improvement in the devices and for the most part they are reliable and well accepted by men who are willing to undergo surgery to enable them to have coitus. The primary side effect is infection at the time of surgery, with an incidence of about 3%. Studies report that the penile prosthesis is effective in diabetic impotent men with low-complication rates [153, 154].

Future Directions in Diabetic Erectile Dysfunction

ED is commonly associated with DM, and each disease process by itself incurs debilitating consequences. DM 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 DM-related changes observed in ED and bladder function, except in young men

with a short duration of DM, are permanent and require medical therapy to ameliorate the symptoms. 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 DM is related to the duration and severity of hyperglycemia and its complications, aggressive tight metabolic control from the onset of disease is essential and prevention of DM is key to avoiding ED.

A possible new therapy to treat the ED associated with DM is the successful transfer of the Maxi-K gene in both the aging and the diabetic rat models that results in normalization of erectile function. Those studies have led to the formation of a company Ion Channel Innovations, LLC which has begun the first human trial of hMaxi-K gene transfer in males with ED [155]. In this completed phase I trial that enrolled 20 men, the safety and tolerability of escalating hMaxi-K doses were assessed. Some men were given doses that were known to be ineffective as a component of the phase I safety trial. 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 doses of 5000 and 7500 μg of the product, clinically significant responses were noted and maintained through the 24-week study period. This successful phase I trial has led to an ongoing placebo controlled two dose phase II trial to evaluate the efficacy of this unique gene therapy. There are no other new modalities in clinical trials at this time.

Summary

Recognized since antiquity, DM has become ubiquitous in many developing and newly industrialized countries. Although the effect of DM 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 DM on male sexual function is emphasized by the fact that more than 50% of patients with DM have ED. The most common causes of diabetic ED include autonomic neuropathy and vascular abnormalities often associated with DM. 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 modulating SM contractility through the contractile apparatus, gap junctions, and potassium channels at the molecular level. We are working toward deciphering the mechanisms governing penile SM relaxation and contraction to help guide novel therapeutic options.

Several therapeutic options are offered for ED: medical therapy such as oral PDE5 inhibitors, intracorporal 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 DM and thus the eradication of its associated comorbidities such as ED.

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