Diabetes and Erectile Dysfunction

John Gore, MD and Jacob Rajfer, MD*

Address
*University of California, Los Angeles, Department of Urology, 10833 LeConte Avenue, Room 66-124, CHS, Los Angeles, CA 90095, USA.
E-mail: jrajfer@ucla.edu

Many diabetic men suffer from erectile dysfunction (ED). The etiology of diabetic impotence is complex, with neurogenic, vasculogenic, and disordered local neuroeffector regulatory mechanisms contributing to the pathology of ED. The introduction of oral phosphodiesterase-5 inhibitors has revolutionized medical therapy for ED. These drugs have become the primary initial treatment for ED, although the medications are less efficacious in diabetic than in nondiabetic patients. Treatment often relies on second-line therapies, including intracavernous injections of vasoactive substances and implantation of prosthetic devices. Recent work with animal models has advanced our knowledge of the molecular pathways involved in diabetic impotence, specifically the discovery of the adverse effects of advanced glycation end-products. Further work may elucidate chemopreventive strategies for the management of diabetic patients. This paper reviews the mechanisms and management of ED in patients with diabetes mellitus.

Introduction

Erectile dysfunction (ED) affects an increasing number of men with age. Based on epidemiologic studies, the prevalence of moderate to severe ED increases from 22% to 49% between 40 and 70 years of age [1,2]. This age-related increase correlates with an increase in dissatisfaction with sexual performance.

Diabetic men account for the majority of patients seen in ED specialty clinics [3]. More than 50% of men with diabetes mellitus suffer from ED. Compared with their non-diabetic counterparts, erectile problems affect diabetic men both with an increased prevalence and at an earlier age of onset. Diabetic men have symptoms of ED approximately 10 to 15 years earlier than do men in the general population. Other factors predisposing diabetic males to ED include insulin dependence, poor glycemic control, concurrent tobacco use, and the presence of other vascular manifestations of diabetes.

Recent studies have used validated instruments to assess the quality of life in diabetic men with ED [4,5•].

Compared with non-diabetic impotent men, diabetic men suffer more severe ED, increased dissatisfaction with sexual performance, and an increase in associated depressive symptoms. Furthermore, despite early response to treatment, when followed longitudinally, this response tends to be only transient, with a decrease in some cases back to baseline sexual dysfunction. Within the cohort of diabetic patients, those with more severe ED experience lower acceptance of their diagnosis of diabetes and increased depressive symptomatology.

Because diabetes exerts its end-organ effects through vasculogenic, neurogenic, and local neuroendocrine mechanisms, common treatment modalities for ED have reduced efficacy in diabetic men [6]. Therefore, the evaluation and management of diabetic impotence requires a multimodal approach that includes rigid glycemic control, evaluation of confounding psychogenic factors, and treatment of ED by a specialist familiar with all available treatment options.

Physiology of the Normal Male Erection

Recent advances in our understanding of the physiology of penile erections [7] have led to the development of new and better treatments for ED. The normal male erection requires an intact penile neurologic and vascular system. The paired cavernous nerves originate from the parasympathetic chain at S2-S4, and in conjunction with the somatic pudendal nerves, incite the neurovascular mechanisms responsible for an erection. The primary source of blood supply to the penis is the common penile artery, a branch of the internal pudendal artery. The common penile artery trifurcates into the urethral, dorsal penile, and cavernosal arteries. The cavernosal artery, through the helicine arterioles, is the actual source of blood to the corporal sinusoids.

Upon sexual stimulation, the activation of parasympathetic outflow results in dilation of the arteries and arterioles supplying the corporal bodies, in addition to dilation of the corporal smooth muscle. This blood is captured within the corporal sinusoids, increasing intracorporeal pressure to a level at which the subtunical venules are compressed against the inner surface of the tunica albuginea, thereby decreasing venous outflow from the penis. At the time of ejaculation, the ischiocavernosus muscles, which are innervated by the somatic pudendal nerves and surround the crura of the corporal bodies, are stimulated and this compression of the blood-filled corpora further adds rigidity to the erect penis.

At the molecular level, nitric oxide (NO) is the principal neurotransmitter involved in tumescence [8,9]. This unstable molecule is released from the cavernous nerve endings and stimulates the release of cyclic guanosine monophosphate (cGMP) within the corporal (and possibly vascular) smooth muscle cells. Increased intracellular cGMP decreases intracellular calcium, resulting in relaxation of the vascular smooth muscle through a cGMP-specific protein kinase. This protein kinase causes hyperpolarization of the smooth muscle cell and acts to dissociate myosin and actin in the cell's myofibrils, thereby causing smooth muscle relaxation. The effects of cyclic adenosine monophosphate (cAMP) on intracellular calcium levels and smooth muscle relaxation are similar to, albeit less potent than, cGMP.

Detumescence occurs as a result of cessation of parasympathetic stimulation after ejaculation and the breakdown of the second messenger cGMP by phosphodiesterase type 5 (PDE-5) within corporal smooth muscle cells. The phosphodiesterases are a family of proteins involved in various intracellular reactions, of which 11 families have been identified. Although the majority of tissues express multiple phosphodiesterase families, PDE-5 is the predominant isoenzyme present in the corporal bodies. The hydrolysis of cGMP by PDE-5 within the corporal tissue leads to an increase in intracellular calcium levels and causes contraction of the corporal smooth muscle cells. The role of the sympathetic nervous system in this process is questionable. Supposedly, norepinephrine acting on the α_1-adrenergic receptor activates phospholipase C, increases intracellular calcium, and leads to contraction of the vascular and corporal smooth muscle.

Pathophysiology of Erectile Dysfunction in Diabetic Men

Management of diabetic impotence is complicated by the myriad end-organ effects of the disease. Similar mechanisms involved in the micro- and macrovascular complications of diabetes (*ie*, retinopathy, nephropathy, peripheral and coronary vascular disease) are implicated in the pathogenesis of ED in diabetic men. Duplex ultrasonography has demonstrated significant penile arterial insufficiency among diabetic men with ED [10], presumably secondary to atherosclerosis of the internal pudendal artery or branches that perfuse the corporal bodies. Studies of the corpora cavernosa of diabetic rabbits demonstrate intimal and smooth muscle fibrosis and endarteritis obliterans of small helicine arterioles [11]. There may also be a venogenic component secondary to reduced compliance of outflow venules and decreased venocclusion of the corporal bodies.

Patients with diabetes develop neuropathy of small unmyelinated nerve fibers, leading to the clinical manifestations of peripheral neuropathy, postural hypotension, gastroparesis, and neurogenic bladder. Patients with diabetic impotence have a demonstrated latency of the bulbocavernosus reflex [12] and delayed evoked potentials of the pudendal nerve [13,14]. The thermal threshold of penile skin more accurately assesses neuropathic changes in small unmyelinated nerve fibers. Diabetic men have significantly decreased warm and cold thermal thresholds compared to healthy men [15].

Further mechanisms implicated in the pathophysiology of diabetic ED include decreased synthesis of NO by the cavernosal nerve, the presence of reactive oxygen free radicals within the corporal smooth muscle, and the role of advanced glycation end-products (AGEs) on the nervous and vascular systems. Diabetes-induced rats have decreased levels of neuronal and endothelial nitric oxide synthase (NOS) [16], which may lead to impaired NO-mediated smooth muscle relaxation. Elevated glucose levels can lead to overproduction of free radical species and result in smooth muscle dysfunction [17]. AGE formation has been associated with microvascular diabetic complications [18]. These products form as a result of nonenzymatic reactions of intracellular proteins and accumulate within vascular and cavernosal tissue. AGEs can cross-link and inhibit the function of proteins such as NOS, the enzyme that synthesizes NO, and can quench free NO [19]. It has been postulated that AGEs may be primarily responsible for the smooth muscle dysfunction seen in diabetic patients with ED [20]. In animal models, inhibition of AGEs has been associated with the prevention of diabetic complications and the return of erectile function [21].

The role of hypogonadism in the pathogenesis of ED in diabetic men is controversial. Early studies demonstrated decreased testosterone levels in diabetic patients with ED compared to non-diabetic impotent men [22–24]. Furthermore, these men demonstrated improvement in erectile function, subjectively and objectively, with parenteral testosterone therapy. Further evaluation in animal models and human models has shown that this decrease in total testosterone may be related to a decrease in sex hormone-binding globulin [25]. Testosterone circulates in the body both free and bound to albumin and sex hormone-binding globulin. Although total testosterone is depressed in a greater proportion of diabetic impotent men, this does not necessarily correspond to a decrease in bioavailable testosterone (a combination of free testosterone and testosterone bound to albumin). Although hypogonadism can be an important factor in the pathogenesis of ED in diabetic men, it is likely only a contributing factor to those listed earlier in this paper.

Management of ED in these patients is further confounded by diseases associated with diabetes mellitus. Most diabetic patients are hypertensive and have an associated dyslipidemia, both independent risk factors for the development of ED. Management of essential hypertension with a variety of antihypertensive agents can further adversely affect erectile function [26]. Finally, as in most men with ED, a severe psychogenic component may further exacerbate erectile failure. Up to 50% of diabetic men have contributing psychosocial factors that may be improved with therapy [27].

Table 1. Comparison of phosphodiesterase-5 inhibitors: pharmacodynamics and reported response rates

Drug	Pharmacodynamics		Response rate	
	T_{max}, *h*	$t_{1/2}$	All patients, %	Diabetic patients, %
Sildenafil [28•]	1–2	4–6	84	56
Vardenafil [31,50]	0.7–1	4–5	81	54
Tadalafil [33,34]	2	17.5	81	51

Treatment

Initial evaluation of ED in the diabetic patient consists of a thorough medical history and physical examination. Confounding nonorganic factors can be meted out through a careful history, with special attention to psychological stressors and a review of the patient's medication list. Physical examination may reveal other sequelae of diabetes mellitus. The presence of peripheral neuropathy, retinopathy, and neuropathy may prognosticate more severe ED.

Oral phosphodiesterase inhibitors have become the first-line agent in the management of ED. Through modulation of the NO-cGMP pathway, PDE-5 inhibitors potentiate an erectile response by enhancing the effect of NO-mediated smooth muscle relaxation. Most patients are referred to urologists only after failing oral PDE-5 inhibitors prescribed by their primary care provider.

All three available PDE-5 inhibitors have been studied extensively, in non-diabetic and diabetic men. Response rates to sildenafil (Viagra; Pfizer, New York, NY), vardenafil (Levitra; Bayer, West Haven, CT), and tadalafil (Cialis; Lilly-ICOS LLC, Indianapolis, IN) are comparable and demonstrate a consistently poorer response in diabetic men with ED compared with non-diabetic men [28•,29–34]. Table 1 compares PDE-5 inhibitor pharmacodynamics and rates of efficacy. Sildenafil and vardenafil have similar times to maximal drug level in the blood stream (T_{max} = 1 hour) and similar rates of metabolism ($t_{1/2}$ = 4–6 hours). Tadalafil has a slower time to maximum blood levels (T_{max} = 2 hours) than sildenafil or vardenafil, but offers the advantage of a longer half-life ($t_{1/2}$ = 17.5 hours) and therefore a longer window of potential effect. In selected patients, responses have been noted up to 36 hours after taking tadalafil [35].

Adverse events have been reported with the use of all three PDE-5 inhibitors in patients with and without diabetes. Most of the side effects are primarily vasomotor in nature and there seems to be no increased risk for these adverse effects in diabetic patients compared with non-diabetic patients [36•]. These side effects include, but are not limited to, headache, flushing, dyspepsia, visual changes, myalgias, and back pain, and are probably the result of cross-reactivity with other phosphodiesterase enzymes in the body. For example, vardenafil and tadalafil have a lesser affinity for PDE-6, the main phosphodiesterase present in the retina, and do not seem to produce the visual changes that are seen with sildenafil. However, sildenafil is not associated with myalgias and back pain, which may be seen in up to 5% of patients taking tadalafil, a difference attributed to tadalafil's greater affinity for the PDE-11 enzyme.

Because only 50% to 65% of impotent diabetic patients respond to oral PDE-5 inhibitors, a significant group of patients require alternative forms of treatment. Second-line treatment of ED often involves intracavernous injections of vasodilating agents such as papaverine, phentolamine, and alprostadil (prostaglandin E1). Diabetic patients are more compliant with self-injection therapy compared to non-diabetic patients, likely secondary to their familiarity with insulin injections [37]. Although some studies report success rates with intracavernous injections approaching 90% in diabetic patients with ED, response rates for diabetic patients with ED, as with oral PDE-5 inhibitors, are lower than those of non-diabetic patients [38]. Multidrug intracavernous injection therapy offers further improved efficacy by addressing multiple mechanisms involved in erection [39]. When compared with non-diabetic patients with ED, diabetic patients require increasing doses over time to achieve adequate erections. This is most likely related to the chronic progressive nature of the underlying disorder. Some investigators have advocated combining oral and injectable treatment modalities in patients with refractory ED, although no studies have yet evaluated the safety and efficacy of such combination therapy.

Other nonsurgical treatment options for the management of impotence include topical alprostadil cream, intraurethral alprostadil insertion, and a constrictive vacuum erection device (VED). When offered an option, many diabetic men prefer the VED over intracavernous injection therapy [40]. Responses to the VED are independent of penile blood flow. In up to 75% of patients with severe vascular disease and neuropathy, use of the VED may achieve results satisfactory for intercourse [41,42].

When conservative therapy has failed, the only remaining option for these patients may be insertion of a penile prosthesis. In older series, diabetic patients had increased rates of prosthetic infection and sepsis [43]. Rare catastrophic complications have been reported, with gangrene of the penis requiring penectomy [44]. With newer techniques emphasizing rigid operative antisepsis and perioperative antibiotics, recent series have reported equivalent infection rates between diabetic and non-diabetic patients

[45,46]. Infection rates have further been reduced with the use of antibiotic-impregnated inflatable penile prostheses [47]. Current opinion places no increased risk of penile prosthesis implantation in diabetic patients with ED compared with patients with other chronic disease states.

The best treatment for diabetic impotence is prevention. As with other chronic disease states, early detection and aggressive control of diabetes mellitus may prevent long-term complications [48]. Glycosylated hemoglobin levels correlate with the development of retinopathy, nephropathy, and neuropathy in diabetic patients. Similarly, better glycemic control correlates with improved erectile function in diabetic men [49]. Treatment of associated hyperlipidemia and hypertension may further improve erectile function. As more is understood about the role of AGEs, oxygen free radicals, and inducible NOS in the role of ED, new medical therapies may become available that halt the progression of diabetic complications and prevent ED.

Conclusions

Treatment of diabetic impotence requires a full understanding of the involved disease mechanisms. The multi-factorial etiology of diabetic impotence complicates treatment and reduces response rates to all available medical therapies for ED. PDE-5 inhibitors have become the mainstay of first-line therapy. However, up to 50% of diabetic patients with ED fail to respond to PDE-5 inhibitors, and will require second-line therapies and even surgery in some cases. New developments elucidating the molecular mechanisms involved in diabetic complications may lead to novel chemopreventive strategies. Specialists involved in the care of diabetic patients with ED need to be familiar with the gamut of treatment options available.

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