Diabetes and Erectile Dysfunction

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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 arteries, 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 cavernosal 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 α1-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 bulbocavernous 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].