Erectile Dysfunction and Diabetes Mellitus

Konstantinos Hatzimouratidis, MD, PhD; and Dimitrios Hatzichristou, MD
Second Department of Urology, Papageorgiou General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

ABSTRACT

Background: Erectile dysfunction (ED) is highly prevalent, affecting ≥50% of men with diabetes mellitus (DM) worldwide.

Objective: This article reviews current knowledge on the epidemiology and underlying pathophysiology of ED in men with DM, diagnostic modalities, and treatment options.

Methods: A MEDLINE literature search was conducted for articles published in English from inception of the database through November 2008, using the terms *erectile dysfunction*, *diabetes*, *epidemiology*, *pathophysiology*, *phosphodiesterase inhibitors*, *intracavernosal injection*, and *penile prosthesis*. Data on the epidemiology, diagnosis, and treatment of ED were extracted from all relevant articles.

Results: The literature search revealed 685 original articles and reviews, 67 of which were selected for inclusion in this review. DM may cause ED through a number of pathophysiologic changes, including neuropathy, endothelial dysfunction, cavernosal smooth muscle structural/functional changes, hormonal changes, and psychological effects. The diagnosis of ED in men with DM is based on their sexual and medical histories and results of validated questionnaires such as the International Index of Erectile Function. Laboratory examinations are usually limited to testosterone and prolactin levels that may independently contribute to ED because specialized examinations are not necessary in most diabetic men with ED. The first step in the treatment of ED in men with DM includes glycemic control and treatment of diabetic comorbidities. The associated hypogonadism must also be treated; otherwise, pharmacologic treatment may be less efficacious or not efficacious at all. Phosphodiesterase type-5 (PDE-5) inhibitors have revolutionized the treatment of ED, and they are considered first-line treatment, with a mean efficacy rate of 50% and a favorable safety profile. Intracavernous administration of vasoactive drugs is the second-line medical treatment when PDE-5 inhibitors have failed. Alprostadil is the most widely used drug for this condition, but the combination of papaverine, phentolamine, and alprostadil represents the most efficacious pharmacologic treatment option for patients whose ED does not respond to monotherapy. Excellent functional and safety results have been reported for penile prosthesis implantation, and this approach, along with proper counseling, can be considered for selected patients with treatment-refractory ED.

Conclusions: ED is common in men with DM, who represent one of the most difficult-to-treat subgroups of ED patients. PDE-5 inhibitors are the first-line treatment option, followed by intracavernosal injections and implantation of a penile prosthesis. (*Insulin.* 2009;4:114–122) © 2009 Excerpta Medica Inc.

Key words: erectile dysfunction, diabetes, epidemiology, pathophysiology, phosphodiesterase inhibitors.

INTRODUCTION

Erectile dysfunction (ED), defined as the persistent inability to achieve and maintain an erection for successful intercourse, is a major sexual concern for many men.[1] Risk factors for ED include cardiovascular disease, diabetes mellitus (DM), hyperlipidemia, smoking, and obesity.[2,3] ED is associated with depression and has a profound negative impact on the quality of life of patients and their partners.[4] The prevalence of ED is higher in men with DM than in those without DM (age-adjusted relative risk [RR], 1.32; 95% CI, 1.3–1.4).[5] The pathophysiology of ED is multifactorial, and men with DM are one of the most difficult-to-treat subgroups of patients with ED. The aim of this review was to provide an overview of the epidemiology and underlying pathophysiology of ED in men with DM, diagnostic modalities, and treatment options.

METHODS

A MEDLINE literature search was conducted for articles published in English from inception of the database through November 2008, using the terms *erectile dysfunction*, *diabetes*, *epidemiology*, *pathophysiology*, *phosphodiesterase inhibitors*, *intracavernosal injection*, and *penile prosthesis*. Data on the epidemiology, diagnosis, and treatment of ED were extracted from all relevant articles.

Accepted for publication December 5, 2008.

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RESULTS

The literature search revealed 685 original articles and reviews, 67 of which were selected for inclusion in this review.

Epidemiology

ED has been reported to occur in ≥50% of men with DM worldwide.[3,6] ED is usually present within 10 years of diagnosis of DM. The incidence of ED was reported to be higher at each decade of life for men with DM than for men without DM, and up to 12% of men who present with ED were found to have previously undiagnosed DM.[3] ED occurs at a younger age in men with type 1 DM than in the general population, and the incidence of insulin resistance is 3 times higher in men with ED.[7]

In the Health Professionals Follow-Up Study cohort reported by Bacon et al,[5] men with DM had an age-adjusted RR of 1.32 (95% CI, 1.3–1.4) for having ED compared with their nondiabetic counterparts. Men with type 1 DM were at a significantly higher risk for ED (RR, 3.0; 95% CI, 1.5–5.9) compared with men with type 2 DM (RR, 1.3; 95% CI, 1.1–1.5). Furthermore, men with type 2 DM had an increasingly greater risk of ED with increased duration since diagnosis, particularly for men whose DM was diagnosed >20 years previously. Fedele et al[8] reported a 35.8% prevalence rate for ED in a cross-sectional study, ranging from 4.6% for men 20 to 29 years of age to 45.5% for men 60 to 69 years of age. Fedele et al[9] also reported a crude incidence rate of 68 cases per 1000 person-years (95% CI, 59–77) in a subset of 1010 men without ED at baseline who were followed prospectively for 2.8 years. Grover et al[10] reported a 49.4% prevalence of ED in a cross-sectional sample of 3921 Canadian men aged 40 to 88 years who were seen by primary care physicians.

The RR for ED in men with DM increases with coexisting cardiovascular disease, renal disease, diabetic foot, and retinal disease.[8,10] The prevalence of ED differs across subsets of patients with coronary artery disease (CAD) and is an early marker of vascular disease. In patients with established CAD, ED may precede the clinical diagnosis of CAD by an average of 2 to 3 years.[11] Furthermore, several studies suggested that phosphodiesterase type-5 (PDE-5) inhibitors can improve endothelial function in addition to saving the patient's life.[12] ED is present in almost all men with DM-related neuropathy, and it is correlated with glycemic control (based on measurement of glycosylated hemoglobin [A1C] levels).[13]

DM is a major component of the metabolic syndrome, and results of several studies revealed that a high percentage of men with ED also had metabolic syndrome.[14] Esposito et al[15] reported a 26.7% prevalence of ED in patients with metabolic syndrome compared with 13.0% in the control group. In addition to ED, the presence of DM at baseline was significantly associated with all aspects of sexual dysfunction, including sexual drive, ejaculatory function, and sexual satisfaction (all, $P < 0.001$).[16]

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Pathophysiology

DM may cause ED through a number of pathophysiologic changes, including neuropathy, endothelial dysfunction, cavernosal smooth muscle structural/functional changes, hormonal changes, and psychological effects (**Figure**).[17] Although pathophysiologic changes may be more pronounced in type 1 DM than in type 2 DM, functional studies failed to document any differences between the 2 types of DM.[18]

Diabetic neuropathy may be linked to selective neurodegeneration that results in decreased neuronal nitric oxide (NO) synthase activity and diminished NO associated with impaired nitrergic relaxation in the corpus cavernosum.[19] In addition, oxidative damage through the formation of oxygen free radicals may contribute to the neurodegeneration, suggesting that it is an NO-dependent process.[20,21]

Endothelial dysfunction is a major cause of diabetic ED.[22] Hyperglycemia reduces activity of endothelial NO synthase, diminishes the effect of released NO, and decreases oxygen free radicals, including advanced glycosylation end products (AGEs).[23] The ultrastructural changes in the endothelium result in increased penile vasoconstriction due to increased levels of endothelin-1 (ET-1) and upregulation of the endothelin receptors (ETA and ETB) in the corpus cavernosum.[24] ET-1–induced vasoconstriction is linked to the RhoA/Rho-kinase pathway that mediates ED through decreased production of NO in the corpora cavernosa.[25,26]

Structural changes include reduction in smooth muscle content, increased collagen deposition, thickening of the basal lamina, and loss of endothelial cells.[27] Several studies have consistently found a reduction in the relaxation responses mediated by endothelial and neurogenic NO in the corpus cavernosum.[20,28] These findings may be explained by the presence of AGEs, which decrease compliance in the corpora cavernosa and impair smooth muscle relaxation by generating free radicals or reactive oxygen species that react with NO.[29,30]

Levels of total, free, and bioavailable testosterone are frequently low in men with type 2 DM; most of these men have clinical symptoms of hypogonadism, including ED and decreased libido.[31,32] Obesity and age are associated with low testosterone levels in men with DM. Hypogonadism has been associated with metabolic syndrome and insulin resistance. Guay and Jacobson[7] reported a 79% prevalence of insulin resistance in men with ED. Several studies confirmed that men with high testosterone values were more likely than men with low testosterone values to have <3 components of the metabolic syndrome. The reverse association