



Erectile Dysfunction in Men With Diabetes Mellitus

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Diabetes mellitus (DM) affects 18 million Americans and more than 221 million people worldwide. Since type 2 DM, which accounts for 90% to 95% of all diagnosed cases, produces few symptoms before microvascular and macrovascular complications have occurred, about one third of all DM cases are undiagnosed.^{1,2}

Erectile dysfunction (ED) is highly prevalent in men with DM, affecting up to 75% of all men who have the disease.^{3,4} Additionally, recent research has shown that men who have ED are more than twice as likely to have DM as are men without the condition—and the younger the man with ED, the stronger the relationship between the two conditions.¹ The implications of the ED-DM association are twofold. On the one hand, physicians treating patients for DM have an opportunity to inquire about the possibility of ED and, thereby, spare the patient the difficulty of introducing a sensitive subject.³ On the other hand, physicians whose patients present with ED may have an opportunity to diagnose DM in its early stages and encourage patients to seek appropriate care, thus preventing DM complications.^{1,3}

Herein, I will discuss ED and DM, and the relationship to a constellation of clinic factors known as the metabolic syndrome. The mechanisms by which diabetes puts men at elevated risk for ED are outlined and the means by which ED can be managed effectively in the diabetic man are described.

The Predictive Value of ED

From a nationally representative managed care claims database involving 51 health care plans, Sun et al¹ conducted a retrospective cohort study comparing a group

of men with ED (285,436) to a group of men without ED (1,584,230). After controlling for age, region, and seven common comorbid conditions, they found that men with ED were 60% more likely to have DM than men without ED (Figure 1). They concluded that ED was a strong, observable, early marker of DM for men aged 45 or younger and a likely marker of DM for men aged 46 to 65. (It was not predictive of DM for men aged 66 and older.)¹ Furthermore, when Kupelian et al⁵ analyzed data from the Massachusetts Male Aging Study (MMAS), a population-based prospective cohort observed at three points over a 15-year period, they found ED to be predictive of metabolic syndrome in men with a body mass index (BMI) below 25. This finding is significant because, though metabolic syndrome would be expected to develop in obese men, its future development has not been easily predicted in men of normal weight. The recognition of ED as a predictor of metabolic syndrome provides clinicians an opportunity to intervene with preventive lifestyle modifications.

Metabolic syndrome—characterized by dyslipidemia, hyperglycemia, hypertension, and central obesity—is a known precursor to cardiovascular disease and DM. The Kupelian analysis involved 928 men who did not have metabolic syndrome at baseline. Among those with a BMI below 25, a group seldom considered at elevated risk for (CVD) or DM, moderate to complete ED more than doubled the risk of metabolic syndrome (relative risk 2.37), again suggesting that the presentation of ED provides clinicians an opportunity for early intervention in men generally not considered at risk for DM or CVD.⁵

Why DM Raises the Risk of ED

The association between DM and ED was first documented in 1798.¹ Since that time, the etiology of ED in DM has become clearer. Essentially, there are three mechanisms by which DM can produce ED: periph-

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eral neuropathy, vascular disease, and hypogonadism.

It's well established that DM adversely affects not only peripheral nerve function, but peripheral blood flow as well.⁴ Both, of course, have the potential to impede normal erectile function which is contingent upon tissue innervation and perfusion. Burchardt et al⁴, however, specifically investigated the smooth muscle and endothelial changes DM could induce in the corpora cavernosa of diabetic rats. Compared to nondiabetic (control or aged) rats, streptozotocin-treated (diabetic) rats underwent a highly significant reduction in the percentage of both smooth muscle and endothelial cells within the cavernosa, suggesting that diabetes significantly decreases corpora cavernosal density.⁴ This loss may point to an erectile tissue dysfunction independent of neuropathy.

Hypogonadism is known to be a pathophysiologic factor in approximately 12% of the men who have ED.⁶ Normal erectile function requires a threshold level of testosterone, and testosterone replacement is clearly indicated for men with hypogonadism and ED.⁶ Among middle-aged and elderly men, hypogonadism is more prevalent than might be imagined.

When Mulligan et al⁷ measured testosterone levels in 2165 men aged 45 years or older, they found the overall prevalence of hypogonadism (defined as having

a total testosterone level of less than 300 ng/dL or current androgen treatment) to be nearly 39% in this age group. Total testosterone levels ranged from 50 to 1,573 ng/dL, with mean concentrations being 364.8 ng/dL for all patients, 245.6 ng/dL for hypogonadal patients, and 439.9 ng/dL for eugonadal patients (Figure 2). Risk of hypogonadism increased with age (Figure 3). Every 10-year increase in age, elevated risk by 17%.⁷

The relationship between DM and hypogonadism was explored by Stellato et al⁸, who prospectively examined the association between low levels of testosterone and sex hormone-binding globulin (SHBG) and the subsequent development of type 2 diabetes in a cohort of the MMAS.⁸ The researchers interviewed the 1,709 men who enrolled in the study between 1987 and 1989, following up with 1,156 of them 7 to 10 years later. Testosterone and SHBG levels were measured at baseline and used to predict new cases of DM type 2 at follow-up.

After exclusions for baseline diabetes or prostate cancer, 1,096 men remained in the analysis sample, 54 (5%) of whom had a new diagnosis of DM at follow-up. Mean levels of baseline testosterone, free testosterone, and SHBG were significantly lower for these men than for those who had not developed DM by follow-up, demonstrating a strong predictive relationship between these measures and

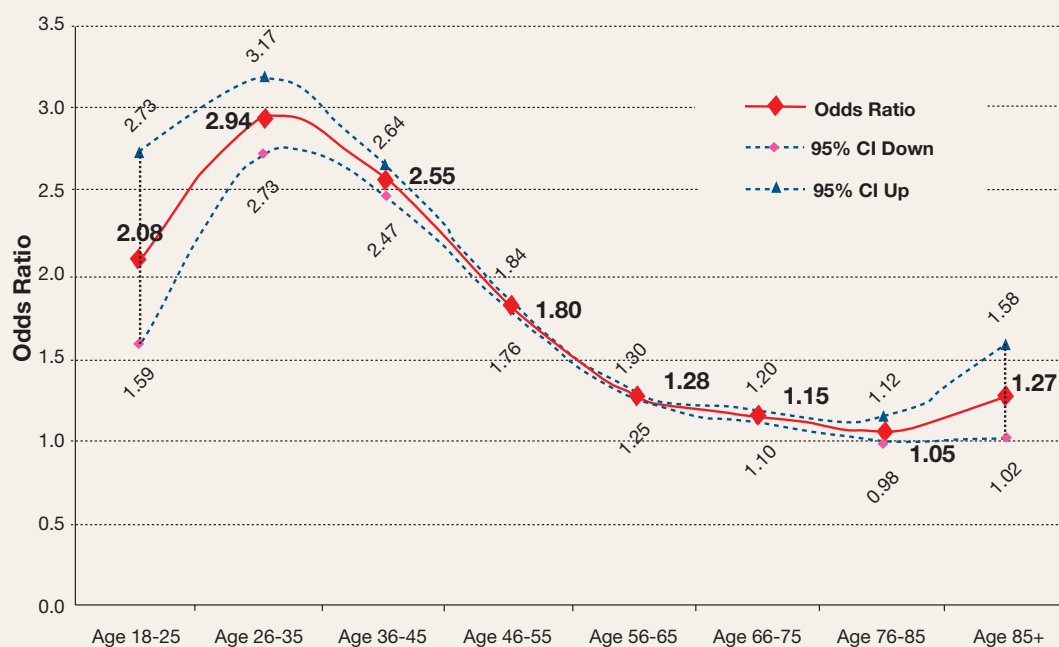
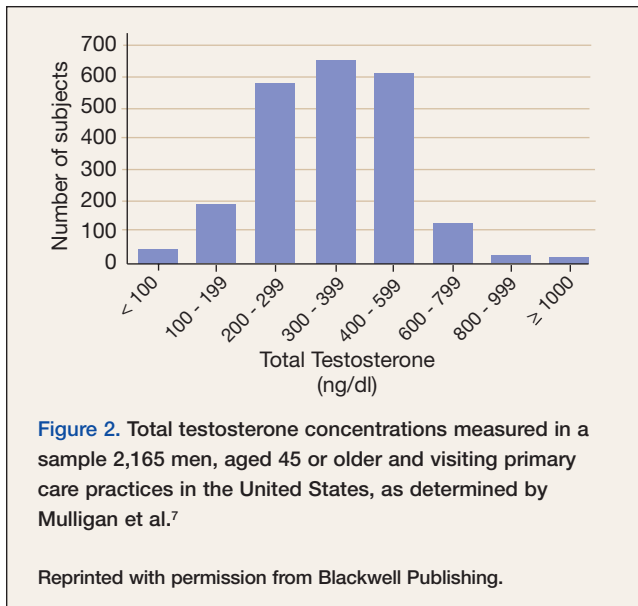


Figure 1. Odds ratios of having diabetes mellitus in the presence or absence of erectile dysfunction (ED) in the retrospective cohort study conducted by Sun et al¹ that compared 285,436 men with ED to 1,584,230 men without ED. By Age Group & with the Same Control of Census Regions and Seven Comorbidities.

CI = Confidence Interval.

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DM that persisted even after multiple logistic regression was used to control for the confounding effects of hypertension, obesity, and other covariates.⁸

The DM harbinger metabolic syndrome also appears to be tied to hypogonadism. When Makhsida et al⁹ conducted a comprehensive MEDLINE review on hypogonadism, testosterone, and metabolic syndrome spanning from 1988 to 2004, they concluded that observational data show hypogonadism to be a fundamental component of the syndrome. Citing interventional studies showing that exogenous testosterone favorably affects body mass, insulin secretion and sensitivity, lipid profile, and blood pressure, they suggest that, as it treats hypogonadism, testosterone therapy has the added potential to slow or halt the progression of metabolic syndrome to overt diabetes or CVD and to prevent such related complications as neurogenic bladder and ED.⁹

Best Treatments for ED in DM

Roughly 75% of men with type 2 DM have ED and, in DM, ED is often more difficult to treat.¹⁰ The mechanism by which phosphodiesterase type 5 (PDE-5) inhibitors improve erectile function is discussed in another article in this supplement (see *First-Line Therapy for Erectile Dysfunction: The PDE-5 Inhibitors* on page 35), but all three FDA-approved PDE-5 inhibitors—sildenafil, tadalafil, and vardenafil—have proven beneficial in treating ED in DM.

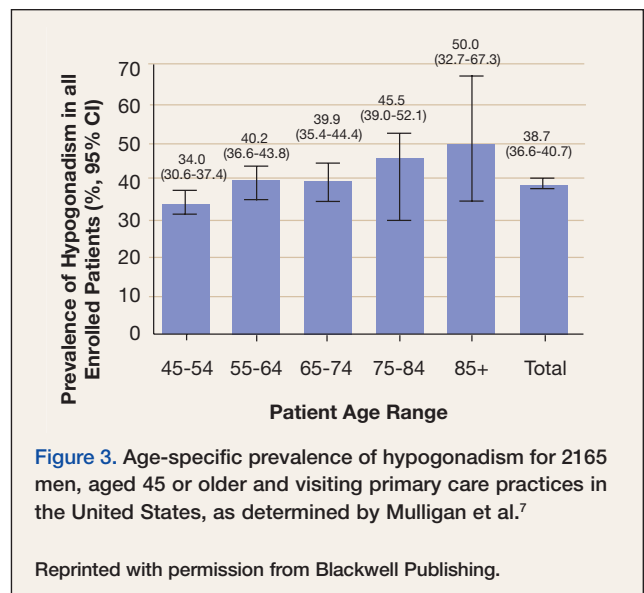
The Sildenafil Diabetes Study Group enrolled 268 men with ED and DM and randomly assigned 136 to receive sildenafil and 132 to receive placebo. Of the 131 in the treatment group who completed the study, 74 (56%) reported improved erections at 12 weeks compared with 13 (10%) in the placebo

group. The proportion of men with at least one successful attempt at sexual intercourse was 61% (71 of 117) in the treatment group versus 22% (24 of 114) in the placebo group.¹¹ Adverse effects were reported by 16% of patients taking sildenafil and these were similar to those reported by sildenafil users without DM—headache, dyspepsia, and sinus congestion and drainage. All were mild to moderate and transient.¹¹

Similarly, in a placebo-controlled study of 216 patients, tadalafil 10 mg and 20 mg improved International Index of Erectile Function (IIEF) domain scores by 6.4 and 7.3 respectively, compared with 0.1 for placebo.¹² The drug was well tolerated, with mild to moderate headache and dyspepsia being the most frequent adverse effects, occurring at a similar frequency as in the general population.¹²

Likewise, vardenafil in doses of 10 mg and 20 mg was shown to be efficacious and safe in a placebo-controlled study of 452 men with ED and DM. After 12 weeks of treatment, both doses significantly increased rates of successful penetration and successful intercourse compared to placebo and improved IIEF scores by 5.9 for the group assigned to receive 10 mg and 7.8 for the group assigned to receive 20 mg.¹³

In men with DM, the efficacy of PDE-5 inhibitors can be further enhanced with more stringent glycemic control (see *Erectile Dysfunction: The Role of Lifestyle Modification* 12). The complications of poorly controlled diabetes (severe neuropathy, vasculopathy, and testosterone deficiency) are known to be associated with poor erectile function. Furthermore, when blood sugar is poorly controlled, the body produces too little nitric oxide for erection to occur. For men with ED and hypogonadism, it may be helpful to combine PDE-5 inhibitor therapy with testosterone replacement therapy.⁶



If PDE-5 Inhibitors are Insufficient

Although the efficacy and tolerability of the PDE-5 inhibitors is excellent across a broad range of ED etiologies, 30% to 35% of diabetic men may have severe pathology and fail to respond to such treatments. If

medical therapy with PDE-5 inhibitors is unsatisfactory, other safe and effective treatments, such as intracavernous injections, transurethral alprostadil, or vacuum tumescence devices, are available.¹⁴

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