

## In Brief

Erectile dysfunction is one of the most common complications of diabetes and also one of the most underdiagnosed. Providers need to understand the pathophysiology of this condition in their diabetic patients and make an effort to diagnose and treat it. By doing so, they will improve their patients' quality of life.

# Erectile Dysfunction in Diabetic Patients

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Sexual dysfunction is a common, underappreciated complication of diabetes. Male sexual dysfunction among diabetic patients can include disorders of libido, ejaculatory problems, and erectile dysfunction (ED). All three forms of male dysfunction can cause significant bother for diabetic patients and can affect their quality of life. Despite this, health care providers often do not specifically ask their male diabetic patients about sexual function. This results in considerable underdiagnosis because patients are often reluctant or embarrassed to initiate discussion of these issues themselves. By not recognizing sexual dysfunction as a common organic sequelae of diabetes that should be addressed and treated, providers are missing an important opportunity to improve their patients' daily existence and quality of life.

While all three forms of male sexual dysfunction can be found among diabetic men, this review will focus on the most common form, ED, because the literature is most mature in this area. Defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance, ED is highly prevalent in diabetic men<sup>1</sup> and is almost always organic in its etiology. Given that many patients feel that their ED is "in their heads" and that "their provider will dismiss any sexual problems they

might bring up,"<sup>2</sup> it may be a relief for patients to learn that their ED is physical, related to their diabetes, and treatable. To this end, the goal of this article is to review the epidemiology, pathophysiology, quality of life effect, and treatment of ED in men with type 2 diabetes.

## EPIDEMIOLOGY OF ED IN MEN WITH DIABETES

A substantial body of literature documents the prevalence of ED in men with diabetes. Unfortunately, the majority of these studies do not distinguish between type 1 and type 2 disease, and, therefore, it is difficult to determine if prevalence rates between the two forms of diabetes differ significantly. Acknowledging this limitation in the literature, prevalence estimates of ED in cross-sectional studies of diabetic populations range from 20 to 71% (Table 1). Most of these studies did not control for severity of disease, duration of disease, or control of hyperglycemia.

The wide range of prevalence rates noted among the studies can be attributed to a number of factors. First, prevalence rates are affected by the sensitivity and specificity of methods used to assess ED.<sup>1</sup> In addition, a number of these studies used medical record review to identify patients with ED, as opposed to anonymous patient reports. It has been shown in other

**Table 1. Epidemiological Studies Reporting Prevalence of ED**

First Author	Year	<i>n</i>	Age Range (years)	Type of Diabetes	Prevalence of ED (%)
Schoeffling <sup>15</sup>	1963	314	ND	ND	51
Ellenberg <sup>11</sup>	1971	200	ND	ND	59
Faerman <sup>62</sup>	1972	299	18–50	1 & 2	40
Kolodny <sup>9</sup>	1973	175	> 18	1 & 2	49
McCulloch <sup>12</sup>	1980	541	20–59	1 & 2	35
Nathan <sup>63</sup>	1986	125	55–74	2	71
Cavan <sup>10</sup>	1987	292	20–59	ND	23
Feldman <sup>64</sup>	1994	52	40–70	ND	28
Klein <sup>1</sup>	1996	359	21–76	1	20
Fedele <sup>5</sup>	2000	9,756	20–69	1 & 2	26/37
Siu <sup>4</sup>	2001	486	21–80	1 & 2	63
De Berardis <sup>6</sup>	2002	1,460	62 ± 10	2	34

ND, no data.

disease states that patients tend to underreport ED when questioned directly by their providers.<sup>3</sup> Therefore, the use of validated questionnaires that are either self-administered in an anonymous, neutral setting or administered by an objective third-party interviewer are preferred.

Finally, prevalence rates will be affected by whether the study population is accrued from a single hospital/clinic setting or from a more general population of men with diabetes. For example, Siu et al.<sup>4</sup> studied 500 Chinese diabetic men (of which 97% had type 2 disease) seen at a single medical clinic in Hong Kong during 1999 and found the overall prevalence of ED to be 63.6%. Contrast this to Fedele et al.,<sup>5</sup> who studied 9,756 diabetic men accrued from 178 diabetes centers in Italy. Among the 8,373 men with type 2 diabetes, only 37% reported ED, considerably less than in the Chinese study.

This disparity is due not only to the setting in which the patients were accrued, but also to the manner in which they were questioned, because data in the Italian study were collected by the medical staff during subjects' visits for medical care, which might have also affected reporting rates. De Berardis et al.<sup>6</sup> used a fairly generalizable cohort of 1,460 Italian men with type 2 diabetes accrued from 114 outpatient clinics and patient lists of 112 general practitioners. However, unlike the other Italian study, they used self-administered, validated questionnaires to assess the prevalence of ED among diabetic men. They found that 34% reported frequent erectile problems, and 24% reported moderate problems, for an overall prevalence of

58%. Depending on how one wishes to define "clinically significant" ED, this is probably a fairly accurate assessment.

Three longitudinal studies have estimated incidence rates of ED in men with diabetes. Unfortunately, none of these studies specifically examined men with type 2 disease. In a cohort of 278 diabetic men with type 1 or type 2 diabetes potent at study entry, the proportion of patients reporting ED at 5-year follow-up was 28%.<sup>7</sup> A follow-up analysis of the Massachusetts Male Aging Study, a community-based cohort of men between 40 and 70 years of age, found that the incidence of ED in the diabetic men was 51/1,000 population-years.<sup>8</sup> This figure was similar to the 68/1,000 person-years crude incidence rate of ED reported in a study of 1,010 men with diabetes.<sup>5</sup> However, new studies need to be carried out in well-characterized populations of men with diabetes in order to better determine the incidence of ED and potential effects of interventions to reduce complications.

Complications of diabetes that are associated with an increased risk of ED include peripheral or autonomic neuropathy,<sup>1,7,9–11</sup> nephropathy,<sup>5,11</sup> and retinopathy.<sup>1,10–12</sup> Modifiable risk factors include glycemic control, hypertension, BMI, and cigarette smoking.<sup>1,10,12–14</sup> No intervention studies have used ED as a primary outcome variable.

#### PATHOPHYSIOLOGY OF ED IN DIABETES

Hypogonadism, autonomic neuropathy, and arterial insufficiency are all associated with a higher likelihood of ED in cross-sectional and longitudinal

studies of men with diabetes.<sup>15–17</sup> Experimental investigation of these observations has been accomplished with both in vitro and in vivo models using animals or human tissue.

Low testosterone levels have been observed inconsistently in STZ-induced diabetic and BB rats.<sup>18</sup> Androgen deficiency in rats is associated with downregulation of the neuronal isoforms of nitric oxide synthase, suggesting a trophic effect of testosterone on peripheral erectile tissues. In humans, androgens play a larger role in sexual interest and motivation (libido) than in erectile capacity itself; penile erection is more resistant to androgen withdrawal than is sexual desire.<sup>19,20</sup>

Relaxation of erectile tissue requires nitric oxide from nonadrenergic-noncholinergic neurons and the endothelium.<sup>21</sup> Penile tissue from diabetic men with ED demonstrates impaired neurogenic and endothelium-mediated relaxation of smooth muscle,<sup>22</sup> increased accumulation of advanced glycation end products (AGEs),<sup>23</sup> and upregulation arginase, a competitor with nitric oxide synthase for its substrate L-arginine.<sup>24</sup> Normal responses to direct smooth muscle relaxants in most of these studies implies that the impairments are due to decreased synthesis, release, or activity of nitric oxide. The fundamental mechanisms mediating these changes are thought to be the same as for other diabetic complications: increased polyol pathway flux, intracellular accumulation of AGEs, activation of protein kinase C, and increased flux through the hexosamine pathway.<sup>25</sup>

Experimental in vivo studies have implicated central and peripheral neuropathy, impaired neurotransmission, and endothelial dysfunction in the pathogenesis of diabetic ED.<sup>26,27</sup> Copulatory behavior and penile reflexes are uniformly impaired 4–12 months after the onset of diabetes in the BB rat.<sup>26,27</sup> McVary et al.<sup>26</sup> found that peripheral neuropathy accounts for only part of the dysfunctional findings, and that spinal sexual reflexes were also severely impaired.

Adequate cavernosal arterial inflow is necessary for penile erection. Arterial morphology,<sup>28</sup> flow,<sup>29</sup> and diameter<sup>30</sup> differ between diabetic and nondiabetic populations with ED. BB and STZ-induced diabetic rats exhibit impairment of endothelium-mediated vascular smooth muscle relaxation,

and proposed mechanisms include changes in the expression, activity, or post-translational modification of endothelial NOS.<sup>31</sup>

Experimental hyperglycemia may also affect cavernosal smooth muscle cell contractile responses. In experimental diabetes, penile smooth muscle has augmented force responses to vasoconstrictors, possibly mediated by changes in expression of protein kinase C and the RhoA-Rho kinase Ca<sup>2+</sup>-sensitization pathway.<sup>32</sup> These changes may promote flaccidity and alter the relaxation responses to nitric oxide. End-stage penile dysfunction may occur as a result of diabetes, with progressive loss of normal cavernosal endothelium and smooth muscle cells from the corpus cavernosum.<sup>33</sup> Replacement by fibrotic tissue may lead to complete erectile failure.<sup>34</sup>

### EFFECT OF ED ON QUALITY OF LIFE IN MEN WITH DIABETES

Although ED is a common complication of diabetes, its effect on quality of life is not well understood. Recent work for the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database demonstrates that in the general population of patients presenting to their urologist, ED negatively affects both general and disease-specific health-related quality of life (HRQOL).<sup>35</sup> While this study provides insight into the detrimental affect of ED on quality of life, the cohort is somewhat selected, in that all of the patients were seen in sexual dysfunction clinics and therefore may have been more likely to be bothered by their condition and to report worse quality of life.

However, population-based studies of ED in prostate cancer survivors also document that ED has a negative effect on general health. Penson, et al.<sup>36</sup> studied HRQOL in 2,306 prostate cancer survivors 2 years after their diagnosis. They noted that men with ED (defined as erections that were insufficient for sexual intercourse) had significantly worse general HRQOL when compared to prostate cancer survivors who were potent. Importantly, this association remained in a multivariate analysis that controlled for 31 other potential confounding variables. Finally, this association was noted in both the physical and mental domains of general quality of life, indicating that ED has a much broader effect on quality of life than one might expect.

While these results in prostate cancer survivors are compelling, one wonders if they are generalizable to diabetic men with ED. Numerous studies indicate not only that the findings in prostate cancer survivors are generalizable to all men with ED, but also that they may underestimate the quality of life effect of ED in diabetic men specifically.

A follow-up study from the ExCEED database compared men with ED and prostate cancer to men with ED without prostate cancer and found that the prostate cancer survivors had worse erectile function but reported better quality of life than those without prostate cancer.<sup>37</sup> The authors hypothesized that the prostate cancer survivors were able to "rationalize" away their sexual dysfunction with the knowledge that they may have been "cured" of their prostate cancer. Clearly, diabetic men could not use the same rationale.

In another study from ExCEED, Penson et al.<sup>38</sup> compared erectile function and disease-specific quality of life of men with ED and diabetes to those of men with ED without diabetes. They found that those with diabetes reported significantly worse erectile function ( $P = 0.004$ ) and intercourse satisfaction ( $P = 0.04$ ) than those without diabetes. Importantly, the diabetic patients also reported that ED had a significantly worse psychological impact on their overall emotional life than did their nondiabetic counterparts ( $P = 0.01$ ). Interestingly, no differences were noted between the two groups in the psychological impact of ED on the sexual experience.

These data indicate that diabetic men are more likely to present with more severe ED than do men in the general population and that ED may have a greater impact on quality of life in diabetic patients.

While these studies document that ED has a unique effect on quality of life in diabetic men, they do not describe the exact effect of ED on general quality of life in diabetic patients. To date, there is a single study that addresses this important issue.

De Berardis et al.<sup>6</sup> assessed general HRQOL in 1,460 men with type 2 diabetes in Italy. Within the cohort, 615 men reported that they never experienced ED, 346 stated that they occasionally had ED, and 449 stated that they frequently had ED. They then compared general HRQOL

among these three groups. In the univariate analysis, they found that degree of ED negatively correlated with general HRQOL scores in all eight domains of the Short Form 36 (SF-36) health survey questionnaire. In the multivariate analysis, ED was not independently associated with physical function, bodily pain, or role limitations due to physical problem scores but was independently associated with general HRQOL outcomes in the domains of general health ( $P = 0.004$ ), role limitations due to emotional problems ( $P = 0.001$ ), vitality ( $P = 0.001$ ), social functioning ( $P = 0.01$ ), and overall mental health ( $P = 0.002$ ). Another study examining the effect of ED on quality of life in hemodialysis patients, more than half of whom had diabetes, also noted an independent, negative effect of ED on the emotional domains of general HRQOL.<sup>39</sup>

Diabetes care providers, while becoming more aware of the high prevalence of ED in men with diabetes, may not appreciate the importance of maintaining erectile function to their patients. A recent study by Rance et al.<sup>40</sup> underscores the fact that diabetic men, regardless of whether they actually have ED, believe that ED has a major impact on quality of life and that it is as important to treat as many other conditions associated with diabetes. In an effort to determine the relative importance of treatment for ED compared to other diabetic complications, they gave 192 consecutive diabetic men and 51 control patients seen at two hospitals a standardized questionnaire that assessed the relative importance of a number of diabetic complications and the patients' willingness to pay per month to avoid a particular complication.

Not surprisingly, they found that diabetic patients rated kidney disease and blindness as the two most important complications of their condition. Diabetic men with ED ranked ED as the third most important complication of diabetes, followed on average in order by foot ulcers, high blood pressure, high cholesterol, migraine headaches, sleeping disorders, and mild indigestion. Diabetic men without ED found ED slightly less important, ranking it behind foot ulcers and high blood pressure, although all three were grouped fairly close together (mean ranks were 4.59, 4.23, and 4.52, respectively). Interestingly, in men both with and without ED, sub-

jects were willing to pay more per month to avoid ED than all other conditions except blindness and kidney disease (mean values for diabetic patients with ED were £50.5, £88.0, and £66.1, respectively). In summary, erectile function is important to diabetic men, and when ED is present, it has a significant negative effect on quality of life.

### TREATMENT OF ED IN MEN WITH DIABETES

ED almost always has an organic or mixed etiology in diabetic men. This often results in diabetic men reporting more severe ED when they present for treatment of this condition. It is not surprising, therefore, to learn that diabetic men's responses to standard therapy for ED differ from those of the general population of men with ED.<sup>38</sup> We, therefore, will now briefly review the literature regarding effectiveness of various ED therapies specifically in diabetic men.

#### Phosphodiesterase Type 5 Inhibitors

In the past 6 years, the FDA has approved three oral agents for the treatment of ED: sildenafil, vardenafil, and tadalafil. All three are phosphodiesterase type 5 (PDE-5) inhibitors and work by potentiating the effect of nitric oxide in the penis. In particular, they block the hydrolysis of cyclic guanosine monophosphate to guanosine 5'-monophosphate, thus enhancing nitric oxide-mediated smooth muscle relaxation, increasing blood flow to the penis and facilitating erection.

To date, there are no studies directly comparing the effectiveness of these three agents among diabetic men with ED, so it is impossible to state that one agent is superior to another in terms of effectiveness in diabetic patients. However, there are a number of studies that compare the individual agents to placebo in diabetic men with ED. For example, Boulton et al.<sup>41</sup> completed a 12-week double-blind, placebo-controlled randomized clinical trial of the effectiveness of sildenafil in 219 men with ED and type 2 diabetes. They found that sildenafil resulted in a significant improvement in the ability to both achieve and maintain an erection adequate for sexual intercourse in men with type 2 diabetes. In a similar study, Rendell et al.<sup>42</sup> randomized 268 diabetic men with ED to receive either sildenafil in a dose-escalation manner or placebo.

At the conclusion of the 12-week study, 56% of the patients in the sildenafil arm reported improved erections, compared to 10% in the placebo arm ( $P < 0.001$ ). Additionally, 61% of patients in the diabetic arm reported at least one successful attempt at sexual intercourse in the final month of the study, compared to 22% in the control arm ( $P < 0.001$ ). Similar randomized studies have documented the effectiveness of both tadalafil<sup>43</sup> and vardenafil<sup>44</sup> in the treatment of diabetes-related ED.

When counseling diabetic men who are considering a PDE-5 inhibitor for ED, it is important to set realistic expectations and explain that studies document that all three agents are less effective in diabetic patients than in the general population of men with ED.<sup>45-49</sup> For additional information, readers are referred to the excellent review of the use of PDE-5 inhibitors in diabetic men by Vickers and Satyanarayana.<sup>50</sup>

#### Vacuum Erection Devices

There are few data specifically relating to the effectiveness of vacuum erection devices (VEDs) in diabetic men with ED. In a single-center study of 44 men with diabetes who choose VED for the treatment of ED in the early 1990s, 75% reported that they were able to achieve erections satisfactory for intercourse with the use of the device.<sup>51</sup> However, the manner in which patients were accrued to this study probably biased its findings, resulting in substantially higher effectiveness rates than are normally observed in clinical practice. A recent review of the use of VEDs in the general treatment of ED notes that satisfaction rates with this therapy are much lower, varying between 20 and 50%.<sup>52</sup>

#### Intraurethral Suppositories

There are no studies specifically assessing the effectiveness of intraurethral suppositories of prostaglandin E1 (PGE-1) in diabetic men. A single randomized clinical trial of the effectiveness of this agent in the general population of men with ED documented that 60% of those who tried this agent were able to achieve successful sexual intercourse.<sup>53</sup> Unfortunately, in clinical practice, this agent appears to be considerably less effective.<sup>54</sup>

#### Intracavernosal Injection Therapy

Unlike intraurethral suppositories, intracavernosal injection (IC) injection

of vasoactive agents such as PGE-1 has consistently been shown to be effective in the treatment of ED in men with diabetes. In a study of 336 men with diabetes-related ED, 83% of patients reported erections satisfactory for intercourse after IC injection of PGE-1.<sup>55</sup> Unfortunately, 24% of these patients also reported penile pain, one of the most common side effects of IC injection therapy. Other studies have noted similar effectiveness rates.<sup>56,57</sup>

Although a considerable number of patients report penile pain with IC injection therapy, it appears that diabetic men still have high compliance rates with therapy. In one study, 16 of 18 diabetic men continued IC injection therapy for 7 years, compared to 7 of 22 nondiabetic control subjects with ED.<sup>57</sup> One possible explanation for this is that diabetic patients with ED have fewer options than do nondiabetic men with ED, who are more likely to have a successful response to oral PDE-5 agents, as documented in one study.<sup>58</sup> Another explanation is the greater familiarity with needles and injections among men with diabetes than among their nondiabetic counterparts.

#### Penile Implant Surgery

In diabetic patients who fail medical management of ED, penile implantation surgery remains a viable therapeutic option. In a recent review of 372 men who underwent implantation of a three-piece inflatable penile implant, 86% reported that the device was still functional 5 years after implantation, and 79% reported that they used the device at least twice monthly.<sup>59</sup>

Many providers believe that diabetic patients are at increased risk to develop local infection following penile implant surgery. However, two separate studies have failed to demonstrate that diabetic men are at a significantly increased risk for infection following this procedure.<sup>60,61</sup>

In summary, penile implant surgery remains a reasonable and safe option for motivated, diabetic men who fail other medical therapies.

### CONCLUSIONS

ED is a common complication of diabetes that affects patients' quality of life. While the etiology of this complication may be multifactorial in nature, it is clear that it usually has a strong organic component. Because

men with diabetes value their erectile function highly, it is important that providers encourage them to maintain good glycemic, blood pressure, and lipid control to minimize their risk of developing this complication.

For diabetic men who suffer from ED, there are numerous effective therapies available. Providers, therefore, should specifically inquire about erectile function when treating their diabetic male patients and offer treatment as needed.

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