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 sequela 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 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,” 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. 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...
disease states that patients tend to underreport ED when questioned directly by their providers. 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. 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., who studied 1,000 men with diabetes in Italy. Among the 8373 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. 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%. 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. 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. 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, and retinopathy, and arterial insufficiency are all associated with a higher likelihood of ED in cross-sectional and longitudinal studies of men with diabetes. 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. 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.

Relaxation of erectile tissue requires nitric oxide from nonadrenergic-noncholinergic neurons and the endothelium. Penile tissue from diabetic men with ED demonstrates impaired neurogenic and endothelium-mediated relaxation of smooth muscle, increased accumulation of advanced glycation end products (AGEs), and upregulation arginase, a competitor with nitric oxide synthase for its substrate L-arginine. 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, upregulation arginase, activation of protein kinase C, and increased flux through the hexosamine pathway.

Experimental in vivo studies have implicated central and peripheral neuropathy, impaired neurotransmission, and endothelial dysfunction in the pathogenesis of diabetic ED. Copulatory behavior and penile reflexes are uniformly impaired 4–12 months after the onset of diabetes in the BB rat. McVary et al. 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, flow, and diameter 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.31

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 Ca2+-sensitization pathway.32 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.33 Replacement by fibrotic tissue may lead to complete erectile failure.34

**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).35 While this study provides insight into the detrimental effect 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.36 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.37 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.38 compared erectile function and disease-specific quality of life of men with ED and diabetics 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.6 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 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.39

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.40 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-
jicts were willing to pay more per
month to avoid ED than all other con-
ditions 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 dia-
betic 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 dia-
betic men’s responses to standard
therapy for ED differ from those of
the general population of men with
ED.38 We, therefore, will now briefly
review the literature regarding effec-
tiveness 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, vardenafl,
and tadalafl. All three are phosphodi-
esterase 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 guano-
sine 5’-monophosphate, thus enhanc-
ing nitric oxide–mediated smooth
muscle relaxation, increasing blood
flow to the penis and facilitating erec-
tion.

To date, there are no studies direc-
tly 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 an num-ber of studies that compare the indi-
gual agents to placebo in diabetic
men with ED. For example, Boulton
et al.41 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 silde-
nafl resulted in a significant improve-
ment 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.42 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 erec-
tions, compared to 10% in the place-
bo 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 doc-
umented the effectiveness of both
tadalafl43 and vardenaf144 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.45–49 For additional information,
readers are referred to the excellent
review of the use of PDE-5 inhibitors
in diabetic men by Vickers and
Satyanarayana.50

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 inter-
course with the use of the device.51
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%.52

Intraurethral Suppositories
There are no studies specifically assessing
the effectiveness of intraurethral
suppositories of prostaglandin E1
(PGE-1) in diabetic men. A single ran-
domized clinical trial of the effective-
ness of this agent in the general popu-
lation of men with ED documented
that 60% of those who tried this agent
were able to achieve successful sexual
intercourse.53 Unfortunately, in clinical
practice, this agent appears to be con-
siderably less effective.54

Intracavernosal Injection Therapy
Unlike intraurethral suppositories,
intracavernosal injection (IC) injec-
tion 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 satisfac-
tory for intercourse after IC injection
of PGE-1.55 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 effective-
ness rates.56,57

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

Penile Implant Surgery
In diabetic patients who fail medical
management of ED, penile implanta-
tion surgery remains a viable thera-
petic option. In a recent review of
372 men who underwent implanta-
tion 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.59

Many providers believe that diabet-
ic patients are at increased risk to
develop local infection following
penile implant surgery. However, two
separate studies have failed to demon-
strate that diabetic men are at a signif-
cantly increased risk for infection fol-
lowing this procedure.60,61

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 dia-
betes that affects patients’ quality of
life. While the etiology of this compli-
cation 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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