SEXUAL DYSFUNCTION IN DIABETES

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ABSTRACT

Diabetes is an increasingly prevalent problem that has been associated very strongly with sexual problems in both men and women. Diabetes has numerous end organ effects and also exerts a substantial psychological toll which may predispose diabetic people to sexual problems. Erectile dysfunction (ed) is common in men with diabetes; these men tend to present with more severe and refractory ed compared to non-diabetic peers. While ed is the best-established diabetes-related sexual dysfunction, ejaculatory and sexual desires issues may also occur in men with diabetes. Women with diabetes are also at risk for sexual dysfunction. Sexual health inquiry is an important aspect of diabetes care. Importantly, lifestyle change and close management of diabetes has been associated with improvements in sexual function.

INTRODUCTION

Diabetes mellitus (DM) may lead to disruption of normal sexual function in both men and women via diabetic-induced end organ damage and psychological stress. There is a strong association between diabetes and erectile dysfunction (ED) in men; ED is the best studied sexual dysfunction but the sexual health ramifications of diabetes extend well beyond erectile pathophysiology. In the Endotext chapter on Male Endocrinology “Medical and Surgical Therapy of Erectile Dysfunction”, Shindel, et al review the pathophysiology, work-up, and treatments for erectile dysfunction of any cause. In this chapter, we will focus specifically on sexual dysfunction in people with diabetes, with particular emphasis on practical information for clinicians.

EPIDEMIOLOGY

Sexual dysfunction is a common problem that is particularly prevalent in men and women with diabetes. The presence of sexual dysfunction in type I diabetes has been associated with markedly lower quality of life and psychological distress (1). While, the incidence of sexual problems increases with age (particularly in men but also in women), this is driven primarily by comorbid conditions associated with aging. Examples include smoking, heart disease, high blood pressure, high cholesterol, and diabetes (2). The prevalence of ED in men with diabetes is approximately three and a half times higher than in the general population (3,4). ED may also be the presenting symptom for DM and may predict later neurologic sequelae (5).

PATHOGENESIS

The pathophysiology of ED in DM is multifactorial, consisting of both vascular, hormonal, and neurologic insults (6). Diabetic neuropathy may impair autonomic and somatic nerve processes essential for erections. Diabetes is also associated with impaired relaxation of cavernosal smooth muscle due to endothelial-derived nitric oxide induced by glycosylation products (7-8). A

variety of serum markers (e.g., E-selectin, Interleukin-10, reactive oxygen species) have been linked to diabetes-related ED. The clinical utility of these remains ambiguous but they may have future utility as biomarkers for incipient ED pending further study (9).

New evidence has suggested that men with diabetes may also be at increased risk of low serum testosterone levels (10,11). The etiology of low T in diabetic men remains unclear but may be secondary to a decline in the levels of pituitary hormones responsible for stimulating testicular production of testosterone (12). Low levels of testosterone may lead to a decline in sexual desire and, directly or indirectly, to ED (13).

Men with diabetes should be screened for the presence of low testosterone by checking serum total testosterone. Sex hormone binding globulin and albumin may also be tested to permit assessment for free and bioavailable testosterone (14). The clinical utility of free and bioavailable testosterone remains controversial. The most recent guidelines on testosterone issued by the American Urological Association do not recommend use of free or bioavailable testosterone in clinical decision making (10). The most recent Endocrine Society Guideline states that free/bioavailable testosterone may be worth assessing (via equilibrium dialysis or an accurate estimator) in men with symptoms and low-normal total testosterone (14).

Testing for hypogonadism should be performed in the morning hours (between 8 and 11 AM) when serum testosterone is highest (14). The appropriate assay and biochemical cut-off values for “low” testosterone are controversial; generally speaking, symptoms of hypogonadism are progressively more common in men with total testosterone levels less than 320 ng/dL and free testosterone levels lower than 64 pg/mL (15). When assessing a patient with a single report of low testosterone, providers should consider confirmatory testing to include repeat testosterone as well as pituitary hormones (FSH, LH, and prolactin) to rule out central causes of hypogonadism (10,14). Only those patients with biochemically low testosterone AND symptoms potentially referable to hypogonadism (decreased libido, ED, fatigue, decreased bone mineral density, depressed mood, etc.) in which alternative etiologies for symptoms are not readily apparent should be considered for treatment (14).

TREATMENT OF ED WITH PHOSPHODIESTERASE TYPE 5 INHIBITORS (PDE5I)

The treatment of ED in general was revolutionized by the introduction of the PDE5 inhibitor (PDE5I) class of medications. The first of PDE5I to obtain United States Food and Drug Administration (FDA) approval was of sildenafil (Viagra®), followed by vardenafil (Levitra®/Staxyn®), tadalafil (Cialis®), and avanafil (Stendra®).

All PDE5I are dependent on function of the NO/cGMP pathway. Sexual stimulation provokes the release of nitric oxide (NO) from cavernous nerves and endothelial cells. NO leads to activation of guanylate cyclase, which catalyzes the transformation of GTP to cyclic guanosine monophosphate (cGMP). By a variety of downstream mechanisms, cGMP triggers decreased intracellular calcium with subsequent relaxation of actin/myosin cross bridges and penile smooth muscle relaxation. cGMP is deactivated by conversion to 5 prime guanosine monophosphate, a process mediated by phosphodiesterase type 5 (PDE5)- the predominant functional PDE type found in the penis (16).

PDE5I block the inactivation of cGMP, leading to persistently elevated levels of cGMP and continued smooth muscle relaxation (16). Since the release of NO is mediated by both neuronal and endothelial Nitric Oxide Synthase (NOS), neuropathy and endothelial disease (as may occur with diabetes) blunts the efficacy of PDE5I. This is confirmed clinically as men

with diabetes have a poorer response overall to PDE5I than men with ED of other etiologies.

A prospective, multi-center, randomized, controlled, double-blinded (RCDB) trial of vardenafil in men with diabetes was carried out by Goldstein, et al (17). The study consisted of 430 men with chronic ED, a hemoglobin A1c (HbA1c) of <12%, and no other serious confounding causes of ED (e.g., radical pelvic surgery, spinal cord injury, etc.). Additionally, patients were excluded if they had unstable coronary disease or other contraindications to PDE5I use. The patients were evaluated using the erectile function (EF) domain of the 15 item International Index of Erectile Function (IIEF), 2 diary questions regarding the patient's ability to penetrate (SEP2) and have successful intercourse (SEP3), and a global assessment question (GAQ) about whether or not the treatment had improved their erections. There were statistically and clinically significant improvements in all of the evaluated endpoints, with most of the improvements demonstrating a dose-relation. With 20 mg of vardenafil, the EF score was 19 (out of a total possible of 25) and 54% of men were able to complete intercourse, with an overall responder rate (as measured by the GAQ) of 72%. The effect was attenuated in patients with severe underlying ED but improvement remained significant. There was no correlation noted between different strata of HgA1c levels. The drug was well-tolerated with few patients discontinuing the study due to adverse side-effects.

A similar RCDB trial of tadalafil in men with diabetes was performed by Saenz de Tejada, et al (18). A total of 191 patients completed this study; evaluated parameters were very similar to the vardenafil study above. Exclusion criteria were also similar to the vardenafil study, except that patient with hypertension and hypercholesterolemia were also excluded in the tadalafil study. As in the vardenafil study, statistically and clinically significant improvements were noted in all of the evaluated parameters for men using tadalafil, regardless of severity of underlying DM or level of HgA1c, with an overall responder rate (as assessed by GAQ) of 64% by those using 20 mg. The drug was also well-tolerated with few discontinuations.

A unique study from Denmark attempted to assess the "real-life" use of sildenafil in men with diabetes and ED in terms of how many patients wanted to try an agent, how many were eligible to do so, and how efficacious the medicine was (19). Examining a population of 326 men seen in an outpatient diabetes clinic, 192 (59%) self-reported ED and 187 of these were over 40 years old. Of these 187 patients, 79 (42%) were excluded because of medical or pharmacologic contraindications to sildenafil use. A further 63 patients either declined to participate in the study or did not respond. This left 45 patients for the study (23% of those patients with self-reported ED). Of these, 10 dropped out due to lack of sexual partner and 2 others without recorded reason. Sixty-one percent of the remaining patients self-titrated to a maximum dose of 100 mg. Of the 33 patients remaining, 36% noted consistent improvement, 27% noted variable improvement, and 36% felt they had no improvement; overall, 54% felt that the medicine had met their expectations. Essentially, just 18 of 187 (9.6%) men over age 40 with DM and ED felt that the medicine met their expectations. This real-world experience should inform conversations regarding PDE5i efficacy in men with DM and ED.

In 2008 the US Food and Drug Administration (FDA) approved low-dose (2.5-5 mg) tadalafil as a daily treatment for ED. Hatzichristou et al. enrolled 298 men with diabetes (89% type 2) and ED in a RCDB lasting 12 weeks and assessed clinical response using the sexual encounter profile questions 2 and 3. At baseline 38%, 42%, and 32% of men reported the ability to attain an erection sufficient for vaginal penetration (SEP2) in the placebo, 2.5 mg, and 5 mg groups, respectively. The percentages of men in the same groups able to maintain erection until the completion of satisfactory intercourse (SEP3) were 20%, 20% and 16%, respectively. At the completion of the study, men treated with either the 2.5 mg or 5 mg dose of tadalafil manifested greater improvements in

SEP 2 (increase from baseline of 5%, 20%, and 29%) and SEP3 (28%, 46%, 41%). The lower success rate in the 5 mg group was likely accounted for by relatively worse diabetic disease at baseline in that group. Patients treated with tadalafil reported improvements in erection (based on IIEF scores) irrespective of baseline IIEF scores. Patients were significantly more likely to prefer tadalafil treatment compared to placebo (20).

In addition to daily dosing as an alternative to on-demand dosing for PDE5I, there has been great interest in recent years in the use of PDE5I not just as a therapy to produce erections but as a means to halt or even reverse the penile tissue damage that leads to ED. Studies in animals with a form of experimentally induced diabetes most similar to diabetes mellitus type 1 have demonstrated enhancement of erectile function and preservation of penile tissue health when treated with either vardenafil or SK-3530 (a novel PDE5I that has not yet been approved for routine in humans) (21,22). A preliminary study of routine dose sildenafil vs. placebo for 4 weeks in 292 men with type 2 diabetes and ED revealed some improvements in blood tests used to measure oxidative stress in men treated with sildenafil. Unfortunately, there were some differences between the placebo and sildenafil group at baseline and there were no significant erectile function differences after the 4-week course of daily treatment was completed (23). Another study in 20 men with type 2 diabetes but no ED indicated that treatment with sildenafil 25 mg three times a day led to improved vascular function and a decline in blood markers for various types of inflammation and oxidative stress. The ultimate clinical relevance of these findings is unclear (24).

These encouraging preliminary results will require further assessment before the routine use of PDE5I for reversal of tissue damage can be recommended routinely. A degree of caution is required since, despite a series of encouraging pre-clinical animal studies, routine dose PDE5I for the management of ED related to pelvic surgery has not been proven beneficial for recovery of spontaneous erection responses (25,26).

TREATMENT OF ED WITH OTHER MODALITIES

Direct administration of vasodilators to the erectile tissue of the penis is a well-established modality for management of ED dating back more than three decades. Commonly used agents include papaverine, phentolamine, and prostaglandin E-1 (PgE1) (27). These agents are often used as combinations (e.g., bimix or trimix) to reduce the adverse effects of each specific agent**.**

Only PgE-1 has received formal FDA approval for management of ED. Intracavernosal PgE1 injection therapy in men with diabetes and ED was evaluated in a large, multicenter trial by Heaton, et al (28). Over 300 men entered the trial; 83% completed the titration period and proceeding to home use. Of those patients using the medication at home, 79% required 30 micrograms/dose or less, and 72% remained satisfied with the initial dose during the follow-up period (6 months). There were 2 instances of **priapism** (sustained erection of greater than 4 hours unaccompanied by sexual stimuli) neither of which required intervention, 1 patient developed a penile nodule, and 24% of patients reported penile pain with injection; the pain led to patient drop-out in 5% of the treatment group. A smaller, more recent study with longer follow-up (10 years) found that men with diabetes and ED using penile injections tended to shift towards decreased frequency of use but preferred stronger agents (mixtures of alprostadil with papaverine and/or phentolamine), with men with type 1 diabetes and ED stabilizing their doses within 5 years and men with type 2 diabetes and ED stabilizing within 9-10 years (29).

Prostaglandin may also be administered via an intraurethral route; the Medicated Urethral Suppository for Erections (MUSE®) is a urethral prostaglandin suppository. This treatment has FDA approval and has been used with some success by men with ED. Side effects include urethral burning, pain, and irritation of the sexual partner's mucous membranes (30).

In patients for whom injection or intraurethral therapy does not work vacuum erection devices (VED) may be useful. There is a paucity of data specifically evaluating the use of VED in men with diabetes and ED but the drop-out rate for patients is generally quite high, even for patients who are able to achieve a rigid erection with the device. One subset analysis found that despite a good response (i.e., firm erection) using VED, only 50% of those couples found the treatment to be satisfactory. This may be due to difficult operating the device and/or a feeling that it is a cumbersome interruption of sexual activity. Possible local side effects include petechiae (small red dots from broken capillaries), a feeling of having a cold penis, and abnormal sensation of ejaculation (31). Many men also report that their erectile rigidity is sub-optimal with the VED.

PENILE PROSTHETICS

Penile prostheses are an excellent option for diabetic men with ED refractory to medical management and/or those who cannot tolerate medical management of ED. Prosthesis surgery is irreversible in that the corporal tissue is permanently altered; if the prosthesis is removed without replacement complete ED will almost certainly result. While a variety of exotic materials, flaps, and grafts have been used in the past, most contemporary prostheses are either hollow silicone cylinders that are inflated with saline via pump action or semi-rigid rods (32,33). Of all modalities for management of ED, prostheses have the highest satisfaction rates, with 2 large studies demonstrating greater than 95% satisfaction (34,35). While this high rate of satisfaction is encouraging it must be understood that the population of men who are motivated enough to undergo surgery for erectile function may not be representative of the larger population of ED patients.

Although some studies suggest that elevated HbA1c levels may predict a higher rate of infections in men with diabetes having penile prosthesis surgery, more recent studies refute this (36). A large study from Wilson, et al demonstrated that neither diabetic status nor preoperative HgA1c were risk factors for prosthesis infection. A more recent study confirmed that elevated HbA1c is not a risk factor for infection; however, short-term poor glucose control (defined as morning fast glucose levels >200 ng/ml) was associated with more complications (37,38).

EXPERIMENTAL THERAPIES FOR ED

Low-intensity shock wave therapy (LiESWT) has attracted great interest over the past decade as a novel treatment modality for ED. A number of randomized controlled studies in the general ED population have suggested modest but significant short-term benefit with minimal to no side effect profile (39).

A pooled analysis from 5 double-blind, sham-controlled trials of LiESWT reported on 61 men with diabetes and ED responsive to PDE5I and another 48 men with diabetes and ED NOT responsive to PDe5I. Clinically significant improvements in erectile function were noted in 80%, 77%, and 66% of the PDe5I responsive treated patients at 1-, 6-, and 12-months post therapy. Importantly, over half (55%) of treated men who had been non-responders to PDE5I were able to achieve erection sufficient for penetration with PDE5I post-treatment (40).

These encouraging data merit further research, preferably in a dedicated study of men with diabetes-related ED. Despite encouraging preliminary data this therapy remains experimental and is currently not recommended outside a clinical trial setting conducted at no or minimal cost to patients (26).

TREATMENT OF LOW TESTOSTERONE LEVELS

Although there is some controversy over what constitutes a true "low" testosterone level and the best way to measure it, some studies have indicated that men with low levels of testosterone and symptoms consistent with low testosterone (e.g., decreased

libido, decreased energy, depression, anxiety, fatigue, weight gain) may benefit from testosterone replacement therapy. The general efficacy of testosterone in improving sexual function (particularly sexual desire and response to PDE5I in cases of initial failure to respond) in appropriately selected patients has been established (41). In addition to improving sexual symptoms in these men, testosterone supplementation may have beneficial effects with respect to lean body mass and insulin sensitivity in diabetic men with hypogonadism (42,43). A recent small RCDB indicated that 40 weeks of testosterone supplementation did not produce a significant improvement in either sexual desire or erectile dysfunction for obese men with type 2 diabetes (44). A more nuanced finding in a larger population suggested that the testosterone supplementation provides benefit for men with sexual dysfunction and severe testosterone deficiency (defined here as less than 8 nmol/L, approximately 230 ng/dL) who are treated such that trough levels approach 15 nmol/L (approximately 432 ng/dL) (45).

A number of different testosterone formulations are available, including intramuscular injections, transdermal creams/gels, buccal tablets, and subcutaneous depots (see the Male Reproduction Section of Endotext for a complete discussion of testosterone replacement therapy).

EJACULATORY DYSFUNCTION

Men with diabetes may have sexual disorders other than erectile dysfunction. Examples include diminished sexual desire, lack of ejaculation with sexual climax (anejaculation or retrograde ejaculation), and premature ejaculation. Successful antegrade ejaculation depends on the coordination of three neurologic events: seminal emission, bladder neck closure, and contraction of the muscles of the pelvic floor (e.g., bulbocavernosus, ischiocavernous, etc.) (46). In diabetes, derangements of the nerves controlling closure of the connection between the bladder and urethra may disrupt normal ejaculation. In this situation ejaculate is deposited in the innermost portion of the urethra but the connection between the bladder and urethra does not close. Since the bladder neck is open, some or all of the ejaculate may leak backwards into the bladder during the muscle contractions that normally expel the semen from the penis. In the most severe cases there may be total lack of seminal emission. Either of these conditions will impact fertility. It may also be a source of psychological disturbance to the man; indeed, some men report that they are not able to fully enjoy orgasm in the absence of ejaculation.

From a fertility standpoint, sperm may be retrieved from post-ejaculate urine and then used for artificial insemination. Alternative strategies to overcome retrograde ejaculation generally focus on attempts to help the bladder neck close. A variety of pharmacologic agents have also been used, including anticholinergics, antihistamines, and alpha-adrenergics (47,48). Evidence for efficacy of these interventions in management of retrograde/anejaculation is scant.

FEMALE SEXUAL DYSFUNCTION

Our understanding of the medical and physiological aspects of female sexual function is poor relative to our understanding of men's sexual physiology and function. It is recognized that diabetes can be detrimental to female sexuality in a multifactorial manner, including both psychologic and physiologic dimensions (49,50).

In much of the published literature “Female Sexual Dysfunction” is treated as unitary diagnosis in and of itself. It is more appropriate to consider that this overarching term encompasses several specific (and overlapping) concerns related to sexual function.

The International Society for the Study of Women’s Sexual Health describes: (51)

1) Hypoactive Sexual Desire Disorder (HSDD, decreased interest in sex and/or receptivity to sexual initiation by a partner)
2) Female Sexual Arousal Disorder, which can be sub-divided into Female Cognitive Arousal Disorder (difficulty with maintaining mental/emotional arousal responses) and Female Genital Arousal Disorder (difficulty with maintaining genital arousal responses).
3) Persistent Genital Arousal Disorder (unwanted and intrusive feelings of genital arousal)
4) Female Orgasm Disorder (compromise of orgasm frequency or intensity).

There are similarities between the molecular processes that mediate both male and female genital engorgement with arousal although the tissue effects of course differ (e.g., vasocongestion of erectile tissues leads to penile erection in men and vaginal engorgement/transudate in women) (52). Caruso et al (53) undertook a RCDB trial of 100 mg sildenafil in type 1 diabetic women with sexual dysfunction. Of the 28 women who completed the trial, significant improvement was seen in both subjective and objective parameters. Subjectively, arousal, orgasm, and dyspareunia were all improved in those taking sildenafil in comparison to baseline and those taking placebo. Color Doppler ultrasonography was performed on the clitoral arteries, revealing an increase in blood flow in these women. The clinical utility of ultrasonography in the evaluation of women with sexual dysfunction is unclear; these results should be interpreted with caution.

THE IMPORTANCE OF MANAGING LIFESTYLE FACTORS IN TREATING SEXUAL PROBLEMS IN DIABETES

As with most aspects of diabetes care, routine exercise, careful monitoring of glucose levels, and usage of appropriate therapies to prevent hyperglycemia are key to preventing progression of diabetes-induced sexual problems. Weight management and dietary prudence are also critical in the management of diabetes. There is evidence to suggest weight loss may reverse erectile dysfunction in some men. In a study of 65 obese men with ED and the Metabolic Syndrome (MetS, obesity with at abnormalities of blood pressure, abnormal glucose level/diabetes, and abnormal cholesterol levels), eating a "Mediterranean diet" (emphasizing fresh fruit and vegetables) for two years led to normalization of erectile function (as determined by an International Index of Erectile function score greater than 22) in 13 of 35 men compared to 2 of 30 men in the group that did not have dietary manipulation (54).

A similar study in women with sexual dysfunction and MetS showed a significant improvement in mean sexual function (mean increase on the Female Sexual Function Index from 19.7 to 26.1 in the treatment group vs. no change from baseline in the control group). Also noted in both of these studies were improvements in serum insulin and glucose level in men and women who consumed a “Mediterranean” diet (55). A multi-center randomized controlled trial of intensive lifestyle intervention in obese women with type 2 diabetes confirmed that women who had the intervention were: 1) more likely to remain sexually active at one year (83% versus 64% for the intervention versus control group, respectively), 2) improve specific domains of sexual function, and 3) to obtain composite scores on the Female Sexual Function Index that were consistent with low risk for sexual dysfunction (28% of intervention patients versus 11% of controls) (56).

CONCLUSION

Sexual dysfunctions are common in people with diabetes and may arise from a variety of vascular, neurologic, and hormonal derangements. In terms of managing ED, PDE5I are the first-line agents of choice although the failure rate is higher when compared to men with non-diabetic ED. Second and third line options may be considered should PDE5I fail. Sexual problems related to diabetes extend beyond ED to

include sexual desire and ejaculatory dysfunction in men and a variety of sexual concerns in women. In addition to therapy specifically tailored to sexual concerns, management of underlying diabetic condition may markedly improve sexual quality of life in people with diabetes.

SUMMARY

- The cause of ED in men with diabetes is multifactorial, including neuropathy, vasculopathy, and endocrinopathy
- Men with diabetes should be routinely screened for the presence of low testosterone
- Non-ED sexual dysfunctions are common in people with diabetes
- Medical therapies for ED in men with diabetes are not as successful as in men with ED of other etiologies

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