Diabetes-associated Erectile Dysfunction

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Abstract

Erectile dysfunction (ED) is a common complication of diabetes, with a prevalence ranging from 15 to 55%. The basis underlying diabetes-associated ED is multifactorial, involving changes in peripheral nerve activity and alterations in endothelial cell function. Due to the complexity of this pathology, the development of experimental models has been crucial in evaluating and translating fundamental results into clinical diabetes-associated ED. The concept of hard-to-treat patients, such as men with diabetes, is now fully accepted due to the complex mechanisms involved. In these men, the response to common oral treatments with phosphodiesterase type 5 inhibitors (PDE5Is) is far from desired, and maximal doses of the drugs are often needed. In addition, diabetes is commonly associated with other co-morbidities, such as hypertension, hypercholesterolaemia and obesity, clusters of the metabolic syndrome (MetS). ED is considered an early warning sentinel for coronary artery disease, just as endothelial dysfunction is seen as a major risk factor for ED. Testosterone deficiency syndrome, a very common syndrome in diabetes and MetS, has been shown to be an independent determinant of endothelial dysfunction, thus contributing to vascular pathology, including ED. This syndrome should be identified among patients, and therapeutic intervention may be required. PDE5Is may improve erectile function with or without the help of other second- or third-line treatments. Other strategies to maximise the response to PDE5Is include risk factor modification and daily dosing of the drugs, instead of on-demand treatment. However, better understanding of the fundamental molecular mechanisms underlying diabetes-associated ED is essential to improving and developing more effective therapies.

Keywords

Diabetes, erectile dysfunction, endothelial dysfunction, phosphodiesterase type 5 inhibitors, penile nitric oxide release test (PNORT)

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Background and Animal Studies

Diabetes is an increasing disease worldwide, and it is estimated that the number of cases will rise to 300 million globally by 2025.[1] Erectile dysfunction (ED) is a common complication of diabetes and is responsible for a decreased quality of life in diabetic men,[2] who have a three-fold higher risk of ED development compared with healthy individuals. ED may also be the initial presentation of diabetes in 12% of patients subsequently diagnosed with this pathology.[3] In individuals with diabetes, ED occurs at an earlier age, is more severe and increases with disease duration, being approximately 15% at 30 years of age and rising to 55% at 60 years of age.[4] In individuals with diabetes, ED has been associated with the underlying neuropathic condition. However, it seems that as a result of their location, cavernosal vascular endothelial cells (ECs) are the primordial organ affected by this disease. In fact, metabolic derangements induced by hyperglycaemia and increased oxidative stress disable penile EC functional response in order to maintain homeostasis, impairing the endothelium regulatory role on the modulation of vascular- and smooth-muscle (SM) contractile tone, which is crucial for normal erectile functionality. This loss of endothelial ability to vasodilate in response to local and systemic changes is referred to as endothelial dysfunction and recognised as a key feature of diabetes-associated ED.[5] Ageing may also affect the structural and functional properties of ECs and SM, leading to vascular dysfunctions.[6]

Due to its complex pathophysiology, diabetes-associated ED is less responsive to common oral treatments with phosphodiesterase type 5 inhibitors (PDE5Is).[7] Therefore, a better understanding of the fundamental molecular mechanisms involved in diabetes-associated ED is essential to the development of more effective targeted therapies. In addition, diabetes is commonly associated with other co-morbidities, such as hypertension, hypercholesterolaemia and obesity, clusters of the metabolic syndrome (MetS), which are considered independent vascular risk factors (VRFs) of endothelial dysfunction and ED.[8] These VRFs may contribute to loss of endothelium actions in a synergistic fashion and to the exacerbation of penile vasculopathy and severity of ED. More importantly, it was suggested that ED may be not only a clinical manifestation of a pathology affecting the penile circulation but also an early warning sign of a more generalised vascular systemic disorder. In fact, all of the aforementioned VRFs are highly prevalent and frequently co-exist in patients with coronary artery disease (CAD) and ED, with a common denominator of the presence of generalised endothelial dysfunction.[9] Considering ED as a silent indicator of a more general vascular disorder is crucial for the prevention of cardiovascular events in patients with ED and asymptomatic CAD.

Molecular Vasculopathy of Diabetes-associated Erectile Dysfunction – Relevant Studies in Diabetes and Metabolic Syndrome Experimental Models

Animal models, in particular rodents, have contributed a great deal to our understanding of and advances in the field of sexual medicine. In studies of diabetes and ED, the rat has proved a valuable and consistently reproducible model that has significantly advanced our knowledge of male ED. Established rat models of type 1 and type 2 diabetes have been extremely important in elucidating the underlying mechanisms of endothelial dysfunction in ED. They have aided the identification of numerous biochemical molecular alterations that contribute to penile-lining EC injuries, reducing endothelium-dependent vascular and SM relaxation potential. Poor diabetic cavernosal vasodilation is mostly the result of impairment in endothelial nitric oxide (eNO) bioavailability/bioactivity in the vasculature caused by hyperglycaemia, which induces the formation of irreversible advanced glycation end-products (AGEs) and increased oxidative stress. In alloxan-induced type 1 diabetes male rats it was demonstrated that endothelial function is affected by eNO inactivation in the diabetic penis through a specific glycosylation mechanism.[10] In a type 2 diabetes model of Otsuka Long-Evans Fatty rats it was shown that cavernosal vascular function was also disturbed due to alterations in the expression of the vascular endothelial growth factor (VEGF), a pleiotropic molecule that is essential for endothelium homeostasis. It was demonstrated that the expression of VEGF and its receptors was diminished in diabetic corporeal tissue, disabling proper endothelial functionality of the VEGF signalling system and consequently inhibiting the downstream activation of anti-apoptotic intracellular pathways and impairing eNOS activity.[11]

Concordantly, intracavernous therapies with VEGF were referred to improve erectile function in diabetic models by the amelioration of corporeal apoptosis.[12] In addition, in streptozotocin (STZ)-induced type 1 diabetes rats, the most commonly used model for type 1 diabetes studies, it was demonstrated that reactive oxygen species (ROS) formation and increased oxidative stress associated with AGEs cause several cavernosal alterations, including augmented lipid peroxidation, upregulation of superoxide anion (O_2^-) and a decrease in antioxidant levels. The deleterious effects of ROS are supported by evidence that superoxide dismutase (SOD) gene transfer or treatment with antioxidants in STZ–type 1 diabetes animals reduces superoxide production, increases eNO and restores erectile function.[13] Similarly, in the same type 1 diabetes experimental model it was demonstrated that adenoviral gene transfer of eNOS improves erectile responses.[14]

In STZ-induced diabetes it was also shown that the RhoA/Rho-kinase signalling system is involved in the inhibition of eNO production. The vasoconstrictor protein Rho kinase is increasingly expressed in the aforementioned diabetic animals and downregulates eNOS activity, contributing to cavernosal endothelial dysfunction and ED.[15] Because hyperglycaemia is frequently manifested collectively with other vascular co-morbidities such as hypertension, lipidic alterations and obesity, a cluster of conditions that compose the MetS, it seems reasonable to study ED in appropriate models that overall mimic this metabolic deregulatory condition. The detrimental accumulation of VRFs may contribute synergistically to the severity of cavernosal vascular degeneration and ED. Molecularly, VRFs are common to endothelial dysfunction and involve augmented oxidative stress and decreased eNOS/eNO activation/bioavailability. Nonetheless, other pathological elements of MetS may also deleteriously affect additional penile vascular pathways.

In an attempt to elucidate how the combination of several VRFs contributes to cavernosal endothelial dysfunction, Wingard et al.[16] performed relevant studies in obese diabetic Zucker rats, a strain that mimics the metabolic alterations and MetS phenotype. Their report demonstrates that in MetS animals there is also an increase in endothelium-produced Rho-kinase protein, which enhances vasoconstriction-associated mechanisms. However, this was a single study, and further cellular and molecular research is required using established or novel experimental models to unveil additional endothelial-associated pathways impaired by and involved in MetS-related ED.

Translating Experimental Results into Clinical Diabetic Erectile Dysfunction

Experimental models have been crucial in disclosing important vascular molecular mechanisms affected by the noxious actions of diabetes. However, can these results 'translate' to penile endothelial dysfunction linked with diabetes-associated ED in men? As reported for animal models, hyperglycaemia and ROS production have relevant adverse effects in endothelial function and human erectile capability. High glucose levels induce the formation of irreversible AGEs, increased protein kinase C (PKC) activity and overactivity of hexosamine and aldolase reductase pathways.[17] The excessive generation of ROS by the mitochondrial electron transport chain leads to increased oxidative stress, which establishes the link between these pathways with the consequent structural and functional alterations of penile vascular tissue. In fact, increased oxidative stress actions observed pre-clinically seem to have a corresponding effect in human settings. A relationship between oxidative stress and human diabetes-associated ED has been established.

One of the sources of ROS production is circulating monocytes with elevated oxidative activity, which are present in the peripheral circulation of diabetic patients with ED.[18] As observed in experimental models, free radical O_2^- also interferes with eNO bioavailability, propagating endothelial dysfunction and chronically impairing diabetic penile vascular function.[19] One of the mechanisms involved in NO deficiency is membrane lipid peroxidation and defective antioxidant defensive mechanisms, which may contribute to ED development in diabetic patients.[20] These findings therefore reveal a new rationale for the use of antioxidant therapy in the treatment of ED in diabetes patients.[21] In addition, few experimental studies have suggested that endothelial programmed cell death could be involved in the loss of endothelium biological activities.[22,23] Concordantly, our group has recently shown for the first time how apoptosis affects human diabetic corporeal endothelial function, which is an important mechanism in diabetic-associated ED.[24] We reported that cavernosal tissue of diabetic patients with ED has increased endothelial apoptotic cell density (ACD) compared with non-ED individuals without diabetes (see *Figure 1*). Furthermore, we demonstrated that ACD correlates with endothelial function assessed in a pre-operative stage using non-invasive functional tests, such as the penile NO release test (PNORT)[25,26] and duplex scan ecography. In addition, we have established an important threshold between *in situ* ACD values and cavernosal endothelial functionality. In these cases, the combination of corporeal endothelial dysfunction, microvascular lesions in the

penile circulation and ultrastructural changes in the SM and tunica albuginea lead to inadequate filling of the cavernous bodies and an inability to achieve penile rigidity. This condition is frequent in diabetes patients and is called caverno-venous leakage.

Diabetes-associated Erectile Dysfunction

Recent studies are unanimous concerning the role of risk factors for ED. In fact, age, hypertension and duration of diabetes are significantly associated with the presence and severity of ED. Glycated haemoglobin (HbA_{1c}) levels and waist circumference are additional predictors of ED.[27] Increased insulin resistance has also been associated with endothelial dysfunction and impaired NO signalling in corporeal SM.[28,29] Men with the characteristics of MetS, including obesity and physical inactivity, are at an increased risk of ED.[30] In addition, of particular severity for ED is the association of diabetes and smoking.

A considerable body of evidence exists suggesting a link between reduced testosterone plasma levels, type 2 diabetes and insulin resistance. In fact, low testosterone precedes elevated fasting insulin, glucose and HbA_{1c} values and may even predict the onset of diabetes. Traish et al.[31] suggest that androgen deficiency is associated with type 2 diabetes, MetS and increased deposition of visceral fat, which serves as an endocrine organ, producing inflammatory cytokines and thus promoting endothelial dysfunction and vascular disease. Although endothelial dysfunction and oxidative stress are common factors in both type 1 and type 2 diabetes, androgen deprivation and veno-occlusive disorders may play a larger part in ED associated with type 2 diabetes. In fact, type 2 diabetes is associated with components of MetS and provides a unique environment in which ED develops.[32] Testosterone deficiency syndrome (TDS) was shown to be an independent determinant of endothelial dysfunction, thus contributing to vascular pathology, including ED.[33] As TDS contributes to MetS pathologies that adversely affect the endothelium, resulting in multiple vascular injuries, it can also be regarded as a common denominator of the various pathologies affecting endothelium and a central factor in the development of MetS.[34] Many studies have confirmed that testosterone is important in modulating the regulation of erectile function.[35,36] Animal studies have shown that testosterone deprivation reduces intracavernosal pressure. In addition, testosterone deprivation affects erectile function and induces structural alterations in the corpus cavernosum, with veno-occlusive dysfunction.[37,38] Therefore, testosterone treatment may be a valuable option in the management of hypogonadal men with ED.

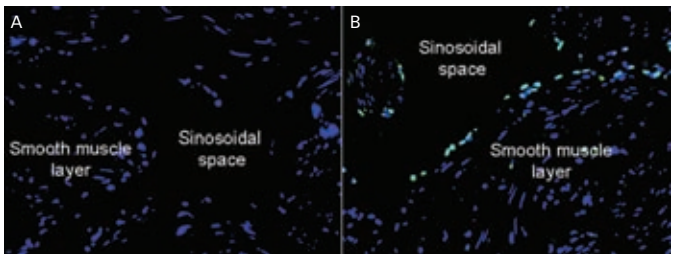
TDS may also be associated with other components of MetS, such as increased triglyceride levels. ED patients with MetS and diabetes also have a higher prevalence of TDS.[39] Interestingly, TDS may play two different roles in type 1 diabetes and type 2 diabetes patients. In type 1 diabetes there is a microcirculation defect in the testes that causes alterations in their vascularisation and a decrease in testosterone production. In type 2 diabetes, and particularly in cases of MetS and/or obesity, there is a switch in the metabolism with the transformation of testosterone in estradiol. Because TDS plays an important role in diabetes, the use of testosterone supplementation has been suggested as part of the treatment regimen, alone or in association with PDE5I.

Evaluation in Diabetes-associated Erectile Dysfunction

Questionnaires and evaluation of ED should be part of any diabetic care facility unit. Many patients with diabetes complain of the lack of attention of their specialist concerning ED, which is an important complication of the disease. In fact, ED is one of the most frequent concerns of men with diabetes. Questionnaires, such as the International Index of Erectile Function (IIEF), particularly the shorter version, IIEF-5, are recommended for easy self-evaluation of the patients regarding the quantification of the decrease or lack of erections (see *Table 1*). In these men, loss of sexual appetite and/or ejaculation problems are frequent. Loss of sexual appetite is commonly linked to decreased testosterone levels, and ejaculation problems occur due to retrograde or absent ejaculations linked to peripheral neuropathy.

In addition to the IIEF, systemic endothelial dysfunction, a key feature of diabetic-associated ED, should also be assessed. The most common non-invasive techniques are Doppler flow-mediated dilation (FMD) of the brachial artery[40] and digital plethysmography.[41] Regarding ED, a more specific non-invasive local test for endothelial function evaluation is the PNORT, which assesses the FMD of the cavernous arteries.[25,26] As stated previously,[24] the severity of diabetic penile endothelial alterations is directly related to a lower PNORT response. In addition, below a certain PNORT index these patients are unresponsive to PDE5Is. PNORT is able to determine patients with low response who will need further evaluation by duplex scan echography after intracavernous injections (ICIs) of vasoactive medications, especially prostaglandin E1 (PGE1), and exploring arterial lesions and

Figure 1: Apoptosis Assay in Control Individual without Diabetes or Erectile Dysfunction (A) and Human Cavernosal Tissue from a Patient with Diabetes and Erectile Dysfunction (B)



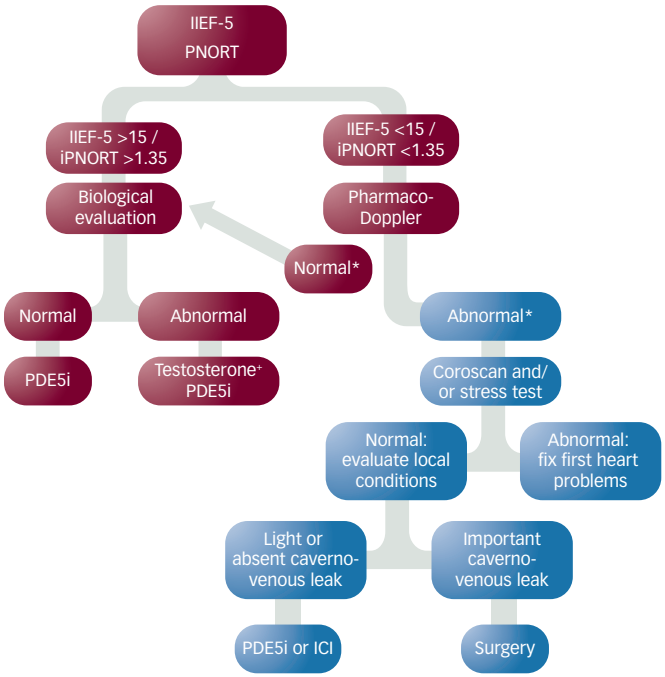
Labelled in green: cavernosal endothelial cells in apoptosis detected by TUNEL assay (24); Labelled in blue: all cavernosal nuclei stained with DAPI (4',6-diamidino-2-phenylindole) (24). Magnification: x200.

Table 1: Basic Evaluation of Erectile Dysfunction in Individuals with Diabetes

1. IIEF-5
2. Check for other vascular risk factors
Smoking habits
Hypertension
Hypercholesterolaemia
Obesity (waist circumference)
3. Biological evaluation
HbA_{1c}
Creatinine
Cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Testosterone (total, free and/or bioavailable)
4-Echo-doppler of penile arteries
PNORT
If abnormal PNORT:
pharmaco-Doppler after intracavernous injection of PGE1;
or electromyography

HbA_{1c} = glycated haemoglobin; IIEF = International Index of Erectile Function; PNORT = penile nitric oxide release test.

Figure 2: Designed Algorithm Based on Penile Nitric Oxide Release Test and International Index of Erectile Function-5 for Therapeutic Decision in Patients with Diabetes and Erectile Dysfunction



**Apply same biological evaluation.*

caverno-venous outflow. In the presence of neurological symptoms, such as decreased sensitivity of the penis and/or retrograde ejaculation, electromyography of the bulbocavernous reflex, dorsal nerve sensitivity and cortical evoked potentials should be studied. Total and bioavailable testosterone levels, the biological status of diabetes and lipidic alterations should always be assessed. Psychological aspects should not be neglected in ED patients. Associated with type 1 diabetes ED is an anxiety profile and frequent neurotic components, which contribute in those patients to performance anxiety. In addition, young patients with type 1 diabetes have an increased incidence of depression.

Is There an Ideal Approach?

Treatment of diabetes-associated ED is multimodal. It is important to make a distinction between prevention in order to avoid or reduce endothelial dysfunction and ED in diabetics, and therapeutic action to treat established diabetes-associated ED.

Prevention

Better glycaemic control would potentially reduce the prevalence of ED and its severity among younger men with type 2 diabetes. In the elderly with type 2 diabetes, ageing and associated VRFs are the major determinants of ED development.[42] Preventative treatment of the underlying co-morbidities is quite important in averting or halting the progression of ED, as well as the correct choice of antihypertensive agents, in order to promote a lesser impact on erectile function.[43] As ED is strongly associated with premature ejaculation and reduced libido, patients with diabetes presenting one of these conditions should be screened for the other.[44] TDS should be evaluated carefully, and testosterone supplementation therapy should be offered according to the recent International Society for the Study of the Aging Male (ISSAM) guidelines.[45]

The recognition of ED as a warning sign for silent vascular disease has led to the concept that a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise.[46] The cardiovascular system of all patients should be assessed prior to any treatment for ED. In this way, men with ED and other cardiovascular risk factors (e.g. age, hypertension, diabetes, smoking, obesity, hypercholesterolaemia, sedentary lifestyle and a family history of premature CAD) should be counselled in lifestyle modification and assigned to one of three cardiac risk levels. Only low-risk patients can be considered for all first-line therapies for ED.[47] In fact, ED is currently considered an early warning sentinel for CAD (a 'potential observable marker'), and endothelial dysfunction is seen as common grounds for the development of both conditions.[48]

Cardiorespiratory fitness was found to be protective of erectile function,[27] and changes in weight loss and exercise were shown to improve endothelial function as measured by brachial FMD and markers of systemic inflammation, and were highly correlated with erectile function improvement. In about one-third of obese men with ED, intervention strategies achieved normal levels of erectile function compared with less than 5% of men in the placebo arm.[49] Obese patients with impaired glucose tolerance could reduce their absolute three-year risk of progression to diabetes from about 35 to 15% by losing 5kg.[50] It is crucial that individuals limit their overall calorie intake, improve their nutrition and become physically active in order to help maintain a healthy bodyweight.[51] The increased oxidative stress associated with obesity may increase free radical formation, which could reduce the availability of NO for target cells. The fact is that obese men with dietary modifications and increased physical activity showed reduced oxidative stress associated with improved NO availability.[52] The use of dietary supplements containing the NO precursor L-arginine and the potent antioxidant SOD in combination with grape extract was shown to increase penile endothelial reaction and improve the erectile response to PDE5Is and/or ICIs.[53]

Concerning this preventative aspect, ED stands for erectile dysfunction, endothelial dysfunction, exercise and diet in prevention, and early detection of risk factors with a view to preventing early death (Princeton II guidelines).[54]

Nevertheless, as ED in patients with diabetes is a ubiquitous symptom with multifactorial causes, both organic and psychological, further larger cohorts of patients need to be screened to establish a true anatomical link between diabetic-associated ED and other cardiovascular diseases.

Therapy

Diabetes-associated ED improvement relies on a comprehensive evaluation of its organic components, mainly neurovascular in type 1 diabetes and vascular and hormonal in type 2 diabetes. Any therapy for ED in patients with diabetes demands an evaluation of the glycaemic status and testosterone level, especially when PDE5Is are to be used. A promising prognostic factor to anticipate therapeutic strategies is the PNORT and IIEF-5 evaluation and the design of an algorithm based on the outcome of these tests (see *Figure 2*). A low index indicating severe endothelial dysfunction precludes a poor response to PDE5Is. Improvement of these lesions to avoid unnecessary treatment failures is mandatory in order to reduce the psychological deterioration of unsuccessful attempts.

Nonetheless, the peripherally acting oral PDE5Is are usually the first-line oral medical treatment for ED in diabetes. Upon sexual stimulation, sildenafil, vardenafil and tadalafil promote prolonged intracellular levels of cyclic guanosine monophosphate (cGMP) by inhibiting this enzyme, thereby improving SM cell relaxation.[55] All PDE5Is are less efficacious in men with diabetes according to the complex pathophysiological mechanisms involved. Generally, patients with diabetes require the maximum dose of each agent taken on demand, i.e. sildenafil 100mg, vardenafil 20mg and tadalafil 20mg. Sildenafil and vardenafil work better on an empty stomach, and tadalafil has a longer half-life, with a window of opportunity of 36 hours, which may aid spontaneity.[56] Adverse effects are generally mild and well tolerated.

PDE5Is are contraindicated in individuals who are on nitrates, due to the risk of profound and dangerous hypotension. However, it is important to stress that no controlled or post-marketing studies of the three available PDE5Is have demonstrated an increase in the rates of myocardial infarction or death. This was observed in double-blind, placebo-controlled trials and in open-label studies (compared with expected rates in the study populations).[57] Although the efficacy of PDE5Is is significantly lower in diabetes, there is an important issue concerning treatment failure due not only to the severity of its pathophysiology but also to the inappropriate use of the medication, unrealistic patient expectations, difficult relationship dynamics, severe performance anxiety and other intrapsychic conflicts and problems of the individual.[58] Fewer than four doses/attempts was the most common factor in treatment failures, followed by insufficient dose titration to the maximum tolerated dose. Timing of intercourse and food instructions are also important. Many patients need to be reminded that these agents should not be considered a 'magic pill' for outstanding sex and that they do not work well without erotic stimulation. Up to 55% of initial non-responders to sildenafil experienced improvement after education.[59] Monotherapy with testosterone appears to be of limited effectiveness in ED but is most promising in younger hypogonadal patients without vascular risk factors.

The combination of testosterone and PDE5Is appears beneficial in men with ED and TDS.[60,61] Blute et al.[62] demonstrated that testosterone therapy can convert over half of men who failed to respond to PDE5Is into PDE5 responders. However, it is still unclear whether men with TDS should be treated initially with PDE5I, testosterone or a combination of both. Different preparations are available, including gel, patches and injections. Gel and patches are the most commonly used preparations, but intramuscular injections can be considered when testosterone levels are significantly low and long-term administration is indicated.

A continuous administration scheme of PDE5Is may also be considered. McMahon[63] treated men with ED with continuous, flexible doses (10 and 20mg) of tadalafil on a daily basis for 12 weeks. Daily tadalafil significantly improved patients' IIEF and sexual encounter profile question 3, compared with on-demand tadalafil. In a study of men with diabetes and ED, once-daily tadalafil 2.5 and 5mg was efficacious and well tolerated, suggesting that this may be an alternative to on-demand treatment for some men, thereby eliminating the need to plan sex within a limited time-frame.[64] In fact, once-a-day therapy with tadalafil in men with diabetes with ED significantly improved various aspects of patient satisfaction. Dissassociating the temporal relationship between sexual intercourse and treatment may be of benefit for some patients, because planning sexual activity around a pill intake is a burden to some couples.[65,66] Preference studies will show whether some patients with diabetes and ED prefer to take daily tadalafil rather than on demand. As ED severity with diabetes correlates with endothelial dysfunction due to impairment in eNO-dependent vasodilatation responses, tadalafil was shown to improve serum biomarkers of endothelial dysfunction, such as C-reactive protein and vascular adhesion molecule-1.[67] The chronic use of tadalafil is therefore quite attractive, as it may ameliorate endothelial dysfunction, as well as improve erectile function. In addition, chronic therapy with tadalafil also improved endothelial function in patients with increased cardiovascular risk, regardless of their ED degree. The benefit of this therapy was sustained for at least two weeks after the discontinuation of the treatment.[68] A chronic schedule also produces a dramatic increase in morning erections, which determines better oxygenation of the penis, thus providing a rationale for vascular rehabilitation.[67] In type 2 diabetes patients, daily sildenafil administration improves endothelial function and reduces markers of vascular inflammation, suggesting that the diabetes-induced impairment of endothelial function may be improved by prolonged PDE5I therapy.[69]

ICIs and transurethral application of vasoactive substances are generally used as a second-line treatment of ED in patients with diabetes. As mentioned previously, ICIs should be considered as first-line treatment when the clinical evaluation shows severe endothelial dysfunction with less chance of PDE5I therapeutic effectiveness. The most common injectable agents include papaverine, phentolamine and PGE1. They may be delivered alone (PGE1) or in association when additional efficacy is needed.[70] PGE1 is the most commonly used agent and can also be delivered transurethrally with lesser efficacy and increased adverse effects. In a heterogeneous group of men with ED, the intracavernous administration of PGE1 was shown to be more effective than the transurethral approach (92.6 versus 61.8%).[71] Diabetes patients, particularly those who are on insulin therapy, have a better and easier acceptance of injections. Compliance is also better compared with non-diabetic men.[72] In a 10-year follow-up period, type 1 and type 2 diabetes patients used a similar number of injections for the treatment of their ED. Interestingly, patients with insulin-dependent diabetes progressed more quickly to the final standardisation treatment than those with non-insulin-dependent diabetes, possibly due to their familiarity with self-injecting and willingness to utilise injection therapy.[73] Mild, short-lasting penile pain is a common adverse effect of the treatment with PGE1, and prolonged erections were reported by 5% of men.[74] Contraindications to ICIs are scarce, including priapism, multiple myeloma and sickle cell disease.

Vacuum erection devices are an additional treatment for diabetes-associated ED. In spite of being universally accepted and not requiring a prescription, they are cumbersome and give an unnatural erection. This approach is overall the most economical therapy for ED. Vacuum erection devices promote satisfactory erections in approximately 70% of men with diabetes.[75] However, up to 30% of patients discontinue their use due to inadequate rigidity, appearance of the penis while using the device (congestion or petechiae), penile pain, coldness, delayed ejaculation and a sense of trapped ejaculate.[76] No specific conditions are contraindicated in the use of vacuum erection devices,

but they should be used with caution in men on anticoagulant therapy or with a history of bleeding disorders, Peyronie's disease and risk factors for developing priapism.

When there is lack of efficacy, contraindication for other first- or second-line therapies or dissatisfaction with other modalities, penile prosthesis is an ideal alternative for ED treatment in diabetes patients. However, prosthetic surgery is irreversible and should be considered the last resort in ED treatment. The inflatable implant offers the ability to achieve a normal erection and flaccidity that cannot be achieved by the semi-rigid implants whereby the penis is not fully rigid or fully flaccid.[77] Of all the modalities for the management of ED, penile implants have the highest satisfaction rates, reaching as high as 95%.[78] Infections remain the most feared complication. Fortunately, with the new devices, which are coated to absorb antibiotics, infection rates are approximately 3% for first-time prostheses. Male diabetes patients are at a slightly higher risk of prosthesis infection,[79] but recent data refute this statement, demonstrating that neither diabetic status nor pre-operative HbA_{1c} are risk factors for prosthesis infection.[80] Malleable implants should be avoided in men with diabetes secondary to their increased risk of erosion. For implant surgery, diabetes patients should have perfect glycaemic levels, and prophylactic antibiotic therapy one day prior, during and after surgery is required.[81]

In summary, there is no ideal approach to treating ED in patients with diabetes. Diabetes-associated ED is more severe and hard to treat. ED in patients with diabetes represents the quintessence of the problems we face with patients suffering from ED and sexual problems. Preventative actions are useful in all cases, particularly in patients with diabetes before they experience distressing symptoms of erectile disability, by avoiding or reducing other risk factors (psychological and/or organic). Different treatments, ranging from medical management to surgical implantation of a penile prosthesis, are the standard at this time, allowing ED to be overcome for any diabetes patient seeking treatment. ■

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