Erectile dysfunction and diabetes: A review of the current evidence-based medicine and a synthesis of the main available therapies

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Abstract

Aim. – This review aimed to provide an update of the epidemiology, pathophysiology and management of erectile dysfunction (ED) in diabetes patients.

Methods. – Data on the management of ED in diabetes patients in the literature were analyzed using Medline, and by matching the following keywords: diabetes; erectile dysfunction; endothelial dysfunction; cardiovascular disease; phosphodiesterase inhibitors; intracavernous injection; and penile prosthesis.

Results. – ED has a higher incidence in diabetic patients. The pathophysiology is multifactorial, involving endothelial dysfunction, specific complications of diabetes and psychological factors. Recent studies have shown that ED is able to predict future cardiovascular events not only in non-diabetics, but also in patients with diabetes. ED could also be a potential marker to screen for silent coronary artery disease. The management of ED has been revolutionized by the discovery of phosphodiesterase type-5 (PDE5) inhibitors, the first-line therapeutic options for diabetic men with ED that are efficient and safe. As a second line, intracavernous injections remain a gold-standard treatment, although a vacuum device can be used as well. In cases of failure, penile prosthesis may be considered. Hypogonadism, commonly found in diabetics, may require identification and treatment. Optimized glycaemic control, management of associated comorbidities and lifestyle modifications are essential in all patients. As ED and diabetes negatively impact male self-esteem, and generate depression and anxiety, the psychological treatment of patients is also likely to be beneficial.

Conclusion. – The aetiology of diabetic ED is multifactorial. Endothelial dysfunction is the link between diabetes-induced ED and coronary artery disease. A global approach is needed for the successful management of diabetic ED.

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Keywords: Diabetes; Erectile dysfunction; Endothelial dysfunction; Cardiovascular disease; Phosphodiesterase inhibitors; Intracavernous injection; Penile prosthesis; Review

Résumé

Dysfonction érectile et diabète : revue de la littérature scientifique et synthèse des traitements disponibles.

Objectif. – Réaliser une revue de la physiopathologie et de la prise en charge de la dysfonction érectile (DE) chez le patient diabétique.

Méthodes. – Une revue de la littérature a été réalisée dans Pubmed avec les mots-clés : diabète ; dysfonction érectile ; dysfonction endothéliale ; maladie cardio-vasculaire ; IPDE5 ; injection intra-caverneuse et implant pénien.

Résultats. – La DE a une prévalence plus élevée chez les patients diabétiques que dans la population générale. La physiopathologie est multifactorielle, impliquant une dysfonction de l’endothélium vasculaire, les complications spécifiques du diabète et les facteurs psychologiques. La DE est un facteur prédictif de survenue d’événements cardiovasculaires chez les diabétiques. De plus, la DE est un marqueur potentiel pour le dépistage d’une maladie coronarienne silencieuse. La prise en charge de la DE a été révolutionnée par la découverte des inhibiteurs de la phosphodiésterase de type 5, qui ont une efficacité et une sécurité prouvées. Ils représentent la première ligne de traitement de la DE chez le patient diabétique. En deuxième intention, les injections intracaverneuses sont proposées. L’implant pénien est une solution de dernier recours. L’équilibre glycémique, la prise en charge des comorbidités et le changement de mode de vie sont essentiels chez ces patients. Enfin, parce que la DE est responsable de dépression, l’accompagnement psychologique ne doit pas être négligé.

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1. Introduction

The US National Institutes of Health define erectile dysfunction (ED) as the inability to achieve, maintain or sustain an erection firm enough for sexual intercourse [1]. Studies have shown an increased incidence of ED in diabetes patients. In addition, ED appears to arise about 10 years earlier in diabetic patients than in the general population [2] and is more severe, decreasing the health-related quality of life. ED is most often a forewarning of cardiovascular disease; thus, the treatment of ED among diabetics is a priority. Diabetic ED is multifactorial in aetiology and more resistant to treatment compared with non-diabetic ED.

The aim of the present review is to provide an update on the epidemiology, risk factors, pathophysiology and management of diabetic ED.

2. Methods

The literature was reviewed using the National Library of Medicine database (http://www.pubmed.gov). A Medline search was performed with special emphasis on diabetes and ED, using combinations of the following terms: diabetes; erectile dysfunction; endothelial dysfunction; cardiovascular disease; phosphodiesterase inhibitors; intracavernous injection; and penile prosthesis. Only articles published between 2000 and 2011 were considered. Also, due to a paucity of randomized data regarding treatment results, articles for this review were selected with regards to the following criteria: evolution of concepts; development and refinement of techniques; intermediate and long-term clinical outcomes; and quality of the study and relevance. Older studies were included selectively if historically relevant or when the data were scanty in more recent publications.

2.1. Epidemiology

Type 2 diabetes, which is strongly associated with changing lifestyles, is reaching pandemic levels. Indeed, the world diabetic population is expected to reach 366 million by the year 2030 [3]. Among diabetic patients, more than 50% have sexual troubles caused by their disease. The incidence of ED is higher in patients receiving diabetes treatment; ED affects 35 to 90% of these patients and more than 65% of such patients who are 40 years old or more [4–10]. In a Massachusetts study of male ageing, men treated for diabetes had a 28% age-adjusted prevalence of complete ED (no erection), which was almost three times higher than the prevalence of complete ED observed in the entire study sample (10%) [2]. The findings also highlighted the extremely deleterious epidemiological link between coronary artery disease (CAD), diabetes and ED.

As the majority of the studies did not distinguish between type 1 and type 2 diabetes, it is difficult to determine whether there are significant differences between the two major types of the disease. Contrary to Fedele et al. [8], two studies reported a similar likelihood of developing ED among patients with type 1 and 2 diabetes after adjusting for age [5,7].

2.2. Pathophysiology of diabetic erectile dysfunction (ED)

The development of ED in men with diabetes is a complex and multifactorial process. The process appears to be affected by vascular and neurogenic causes, endothelial dysfunction, oxidative processes and changes in the nitric-oxide system. Fig. 1 illustrates the multiple mechanisms involved in diabetic ED.

2.2.1. Common risk factors

The risk factors of ED are well known; increasing age and the long-term evolution of diabetic disease [8,10,11] as well as a sedentary lifestyle have been shown to be associated with a higher prevalence of ED not only in the general population, but also in diabetic men [11]. A meta-analysis of population-based studies shows that higher levels of physical activity confer lower risks of ED. The adjusted reduction in the risk of having ED was 58% for men who engaged in greater physical activity and 37% for those who engaged in moderate physical activity compared with men who engaged in little physical activity [12].

There is a link between glycaemic control and ED in men with diabetes in that patients whose disease is poorly controlled are at a two- to fivefold increased risk of ED compared with patients whose disease is well controlled [13,14]. Recent studies have suggested that insulin resistance and the metabolic syndrome may also be strongly associated with the development of ED [15,16]. As is well known, both the metabolic syndrome and insulin resistance (the pathophysiological basis of the metabolic syndrome) are strong and independent risk factors for cardiovascular events and death [17]. Hyperlipidaemia [8,18], hypertension [6,19] and obesity [20] often coexist with diabetes, and are independent risk factors for ED among diabetic men. Other patient risk factors for ED include endocrine disorders, psychological disorders, previous surgery (such as prostatectomy), and the use of alcohol, tobacco and illicit drugs.

Pharmaceutical use is also a factor, as many commonly used drugs contribute to ED [21], including antihypertensives (alpha-adrenergic agonists, beta-blockers, calcium-channel blockers), diuretics (aldosterone antagonists, thiazide diuretics), psychiatric agents (benzodiazepines, butyrophenones, selective...
serotonin reuptake inhibitors, tricyclic antidepressants), digitalis preparations, steroid agents and leuprolide.

2.2.2. Psychological factors

ED is a complex condition that negatively impacts male self-esteem, quality of sexual satisfaction and interpersonal relationships, and also impedes other aspects related to quality of life [4]. A meta-analysis by Anderson et al. [22] demonstrated that diabetes doubled the chances of depression. A longitudinal study by De Berardis et al. [23] reported the strong predictive value of depressive symptoms in the incidence of ED among diabetic men. Moreover, the development of ED has been shown to worsen any pre-existing depressive symptoms, which suggests the possibility of a reinforcing mechanism [24]. Ultimately, all of these factors, as well as partners’ emotions, can generate anxiety and make the condition worse.

2.2.3. Erectile dysfunction (ED) and cardiovascular disease (CVD)

In diabetes patients, the prevalence of ED and CAD is particularly high. Both conditions share many risk factors, such as hypertension, dyslipidaemia, diabetes, obesity and cigarette-smoking. Previous studies have also shown an increased incidence of ED among patients diagnosed with cardiovascular disease (CVD). Several case-control studies have documented an association between ED and CAD in the general population. In particular, Montorsi et al. [25] noted that ED was present before the occurrence of cardiac symptoms in approximately 70% of patients with angiographically proven CAD. Large epidemiological studies have also confirmed the strong association between ED and future cardiovascular events [26–28].

The association between ED and cardiovascular outcomes has also been observed in subjects with documented CVD.
Indeed, ED is a powerful predictor of all causes of death, and the composite endpoint of cardiovascular death, myocardial infarction, stroke and heart failure [11]. In addition to being a potential predictor of CAD, the available data suggest that the severity of ED is correlated with the extent of CAD [29–31].

The first case-control study performed in the diabetic population showed that the prevalence of ED was significantly higher in diabetes patients with angiographically documented CAD than in those with normal arteries on angiography (45.8% vs 15.8%, respectively; \( P = 0.0120 \)) [32]. In addition, the prevalence of ED was threefold lower in diabetes patients without significant CAD on angiography than in those with CAD, which is similar to that observed in the general population. Cross-sectional studies have shown that the presence of ED is associated with a 14.8-fold increased risk of CAD [33], and that 58% of type 2 diabetic men with angiographic evidence of CAD have symptoms of ED before the development of angina [34].

Recently, two separate prospective studies have suggested that the risk of new-onset CVD was even higher in diabetic patients who developed ED. The study by Ma et al. [35] examined the effect of ED on the incidence of CAD in a prospective cohort of Chinese men with type 2 diabetes and no clinical evidence of CVD at baseline. In this cohort of 2306 patients with a median follow-up period of 4 years, 616 (26.7%) had ED at baseline, as defined by the 1992 National Institutes of Health Consensus Conference [1]. During the course of approximately 4 years, the incidence of CAD was greater in men with ED (19.7 per 1000 person-years; 95% confidence interval [CI]: 14.3–25.2 person-years) compared with those without ED (9.5 per 1000 person-years; 95% CI: 7.4–11.7 person-years). After adjusting for other covariables such as age, duration of disease, antihypertensive medications and albuminuria, ED remained an independent predictor of CAD (hazard ratio [HR]: 1.58; 95% CI: 1.08–2.30; \( P < 0.018 \)). Subsequently, the authors recommended that symptoms of ED should be actively sought to identify high-risk subjects for comprehensive cardiovascular and metabolic assessments.

In a similar study, Gazzaruso et al. [36] investigated whether or not ED was a predictor of future CV events and death in type 2 diabetes patients with angiographically documented type 1 silent CAD. During the course of approximately 4 years, 49 of the 291 men recruited for the study experienced a major cardiac event, defined as CAD death, sudden death, non-fatal myocardial infarction, death due to congestive heart failure, unstable angina, need for repeat revascularization, stroke or transient ischaemic attack, or symptomatic peripheral artery disease. The difference in ED prevalence between men with and without major cardiac events was significant (61.2% vs 36.4%, respectively; \( P < 0.001 \)). Throughout further multivariate analyses, ED remained an important predictor of adverse cardiac events and, although diabetic men had a high risk of CVD, the risk was even higher in those who developed ED.

Recent longitudinal studies have shown that ED is able to predict future cardiovascular events in diabetes patients. Baty et al. [37] reported that ED was associated with an elevated risk of all CVD events (HR: 1.19; 95% CI: 1.08–1.32), CAD (HR: 1.35; 95% CI: 1.16–1.56) and cerebrovascular disease (HR: 1.36; 95% CI: 1.11–1.67). Men who experienced ED at baseline and at the 2-year follow-up visit had the highest risk of all for these outcomes.

In addition, in diabetes patients, ED appears to be strongly associated with the presence of silent CAD [33,36,38,39]. Gazzaruso et al. [33] reported a strong and independent association between ED and silent CAD in apparently uncomplicated type 2 diabetes patients. They evaluated the prevalence of ED in 133 men with uncomplicated diabetes and angiographically verified silent CAD as well as 127 diabetic men without myocardial ischaemia on exercise electrocardiography (ECG), 48-h ambulatory ECG and stress echocardiography. The prevalence of ED was significantly higher in the patients with than in those without silent CAD (33.8% vs 4.7%, respectively; \( P < 0.000 \)). Multiple logistic-regression analyses showed that ED, apolipoprotein (a) polymorphism, smoking, microalbuminuria, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were all significantly associated with silent CAD; among these risk factors, ED appeared to be the most effective predictor of silent CAD [odds ratio (OR): 14.8; 95% CI: 3.8–56.9].

Thus, ED may be a potential marker for identifying those diabetic patients to screen for silent CAD. As the diameter of penile arteries is smaller than the diameter of coronary arteries [40], ED precedes diabetic macrovascular complications such as ischaemic heart disease [35,36]. The link between ED and CAD appears to be represented by endothelial dysfunction.

### 2.2.4. Endothelial dysfunction

In men with diabetes, ED is strongly associated with endothelial dysfunction [41,42], a pathophysiological mechanism that has been extensively analyzed.

#### 2.2.4.1. Impaired nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) synthesis

NO is produced by the endothelium of the arteries of the penis and nitrenergic neurons, utilizing endothelial NO synthase and neuronal NO synthase, respectively. NO mediates relaxation of the corpus cavernosum through the formation of cyclic guanosine monophosphate (cGMP) [43]. Superoxide radicals are present in larger amounts in cavernosal tissue, whereas levels of NO synthase are reduced in men with diabetes-induced ED. It is also hypothesized that diabetes impairs the activity of guanylyl cyclase, thereby decreasing the production of cGMP. In addition, oxidative stress or free-radical damage resulting from these vascular insults interferes with the NO pathway and is directly toxic to endothelium, leading to clinically evident occlusive CVD and vascular damage associated with preclinical disease [44].

#### 2.2.4.2. Advanced glycation end-products (AGEs)

Hyperglycaemia in diabetes leads to the formation of AGEs, the products of non-enzymatic reactions between glucose and lipids, proteins or nucleic acids. AGEs are found in greater quantity in the corpus cavernosum of diabetic patients. They form covalent bonds with vascular collagen, an interaction that increases vascular permeability, procoagulant expression, reactive oxygen species and endothelial expression of adhesion molecules [45], thereby accelerating vascular pathology [42,45]. All of these
mechanisms induce oxidative cell damage and quench NO, culminating in decreased cGMP and impaired cavernosal smooth muscle relaxation.

2.2.5. Increased endothelin-1 (ET-1) and endothelin-B receptor-binding sites. ET-1 is a potent vasoconstrictor in the penis, and has been shown to be elevated in the plasma of diabetic patients [46]. There is evidence to suggest that ED in diabetes is linked to an imbalance towards increased penile vasoconstriction as the result of endothelin and its receptors, and ultrastructural changes in the endothelium.

The endothelin transduction pathway is composed of a GTP-binding protein, RhoA, and its effector agent, Rho-kinase. Activation of the pathway suppresses endothelial NO synthase, decreasing the production of NO. Rho-kinase is suggested to be up-regulated in diabetics. It is also proposed that the RhoA/Rho-kinase pathway mediates ED through decreased production of NO in the penis [47].

2.2.5. Diabetic microangiopathy

The association of ED in diabetic men with microangiopathy and neuropathy is now well established. In addition, significant ED is associated with diabetic retinopathy severity independent of age, diabetes duration, macrovascular co-morbidities and cardiovascular risk factors [48]. Diabetic retinopathy is the result of microvascular retinal changes that include endothelial dysfunction and increased vascular permeability. Diabetic retinopathy affects most patients who have long-standing diabetes [49]. Like ED, diabetic retinopathy precedes diabetic macrovascular complications such as ischaemic heart disease [50].

Proteinuria is a well-known measure of diabetic nephropathy and is associated with ED in diabetic men [6,51].

Diabetes is also associated with both peripheral and autonomic neuropathy, both of which may contribute to ED. Innervation of the penis occurs via the dorsal penile and perineal nerves, which carry sympathetic and parasympathetic autonomic nerves as well as sensory and motor somatic nerves. Autonomic neuropathy is strongly associated with ED [52]. The mechanism for ED in autonomic neuropathy lies in the reduced or absent parasympathetic activity needed for relaxation of the smooth muscle of the corpus cavernosum [53]. Parasympathetic tone is also required to decrease norepinephrine levels as well as increase acetylcholine levels, resulting in increased NO synthase activity, which releases NO from both endothelial cells and non-adrenergic, non-cholinergic neurons.

In addition, one study has revealed that ED is a sentinel symptom for the future development of cardiac autonomous neuropathy [54], even though ED secondary to autonomic neuropathy is not significantly associated with cardiac autonomous neuropathy. In diabetic patients, autonomic neuropathy can link ED to overt and silent CAD [33]. Indeed, autonomic neuropathy plays a major role in the development of ED and has been described as an independent cardiovascular risk factor [55]. In addition, autonomic neuropathy can explain the lack of symptoms in patients with asymptomatic CAD.

Diabetes-associated peripheral neuropathy leads to the impairment of sensory impulses from the shaft and glans of the penis to the reflexogenic erectile centre. Motor neurons of the pudendal nerve innervate the pelvic floor muscles, causing contraction of the bulbocavernous and ischiocavernosus muscles, which contributes to the reduction of venous outflow from the cavernous bodies caused by the passive compression of subventral venules in the corpora cavernosa, thus helping to maintain erection. Bleustein et al. [56] reported that, in some diabetic men, dysfunction of the penile nerves precedes neuropathy in the other peripheral nerves.

2.2.6. Hypogonadism

Hypogonadism and ED are epidemiologically associated with, and may even be predictive of, the metabolic syndrome and type 2 diabetes. Men with ED and type 2 diabetes have a higher prevalence of hypogonadism [57], and low testosterone levels are correlated with poor glycaemic control and worsening of ED [58]. Indeed, a recent study reported not only low levels of testosterone, but also its symptoms, in men with diabetes, thereby emphasizing the clinical relevance of the two in association [59].

Visceral adiposity and general obesity, prevalent in men with type 2 diabetes, and the metabolic syndrome can all directly impact testosterone levels. An association between increased body mass index (BMI) and waist circumference and hypogonadism has also been established in men with type 2 diabetes [57,58,60]. In addition, hypogonadism is associated with other components of the metabolic syndrome, such as altered lipid status. Nevertheless, the mechanism of hypogonadism in diabetes is as yet incompletely understood. A low plasma concentration of sex-hormone-binding globulin, the major carrier of testosterone, has been considered to be a cause of low total testosterone in diabetes, which may possibly be related to increased insulin resistance. Another possible mechanism might be increased aromatase activity in visceral adipose tissue, leading to a decrease in testosterone concentration through the conversion of testosterone to oestradiol. The resulting low testosterone levels increase lipoprotein lipase activity, promoting the uptake of free fatty acids into the adipocytes and adipocyte proliferation, thereby further increasing visceral adiposity [44]. It might also be speculated that insulin resistance associated with type 2 diabetes causes a reduction in insulin action in the hypothalamus, leading to hypogonadotropic hypogonadism [61].

2.2.7. Other erectile dysfunction factors

Elevated HbA1c levels and the associated hyperglycaemia in men with type 2 diabetes have been postulated to decrease NO activity and reduce endothelium-dependent relaxation factors, resulting in an increased risk of ED. An HbA1c level greater than 8.1% has been shown to increase the incidence of ED threefold [62].

Frequency of the metabolic syndrome and the prevalence and severity of ED increases with age, as is the case with many conditions, such as ischaemic heart disease and diabetes. ED in men with vs without type 2 diabetes is associated with a marked increase in the probability of developing the metabolic syndrome (88% vs 64%, respectively; \( P = 0.002 \)), central adiposity
and microangiopathy (retinopathy, polyneuropathy and elevated albuminuria) [63]. The presence of type 2 diabetes is significantly associated with severe ED, while the relative risk is as high as 7.1 (P < 0.001) in patients with the metabolic syndrome [64].

Mild elevations of plasma total homocysteine have been identified as an independent risk factor for early atherosclerotic vascular disease [65–67]. Mild hyperhomocysteinaemia has a complex aetiology, including insufficient intakes of vitamins B6, B12 and folate, and genetic factors. The mechanism of premature cardiovascular disease in this context is not precisely known, but may be related to an increased vulnerability to lipid toxicity, the vascular smooth-muscle-cell growth-factor properties of homocysteine, endothelial damage or vasomotor dysfunction, or disorders of platelet aggregation and coagulation. High total plasma homocysteine appears to be associated with ED in patients with adult-onset diabetes [68]. However, the possible role of mild hyperhomocysteinaemia in the development of vasculogenic ED in diabetes is unclear.

2.3. Management of erectile dysfunction in diabetic patients

Despite considerable progress, the treatment of ED in diabetic patients is often difficult due to its multifactorial aetiology. Consequently, a global approach requiring not just one but several treatment modalities is needed. Fig. 2 presents a flowchart describing the management of ED in diabetic patients.

2.3.1. Initial evaluation

A minimal diagnostic evaluation must be performed in every patient [69], including an investigation of the patient’s medical and psychosocial history, to identify problems other than ED sexual problems, while searching for common causes of ED, recognizing reversible risk factors and assessing the patient’s psychosocial profile. The physical examination needs to focus on the patient’s cardiovascular and neurological status, urological examination and signs of hypogonadism. Standard laboratory tests include the patient’s glycaemic and lipid control, and a measure of total testosterone.

In 2005, the Second Princeton Consensus Conference (Princeton II) expanded the recommendations for the management of cardiac patients regarding sexual activity and the treatment of ED [70]. In this update, the guidelines stated that “any symptomatic man who presents with ED that does not have obvious cause (e.g., trauma or post-radical prostatectomy) should be screened for vascular disease and blood glucose, lipids, and blood pressure measurements. Ideally, all at risk but asymptomatic for CAD should undergo elective exercise ECG testing to facilitate risk stratification”. According to the Princeton II guidelines, depending on the presence or severity of conventional cardiac risk factors, subjects should be divided into categories of low (< 10%), intermediate (10–20%) and high (> 20%) risk. Low-risk patients should be reassured and retested within approximately 5 years, and medications for ED can be prescribed without the need for additional tests. Men at intermediate risk may benefit from additional non-invasive tests aimed at better defining the presence and extension of subclinical coronary atherosclerosis, whereas high-risk patients need to undergo further cardiological assessment and receive aggressive treatment for these risk factors. In this latter group of patients, treatment of ED should be deferred until a full cardiological assessment has been performed. Based on these guidelines, a man with ED and no cardiac symptoms is a cardiac or vascular patient until proven otherwise.

2.3.2. General measures

There are general measures that can significantly improve erectile function. The first step in the treatment of ED is to correct the modifiable risk factors for atherosclerotic vascular disease. In this case, patients should be encouraged to quit smoking, reduce their alcohol intake and give up recreational drugs. Some studies have also shown that increasing physical activity and losing weight may be of benefit to sexual function [71,72]. In fact, lifestyle interventions improve endothelial function and NO bioavailability, and may have beneficial effects on ED via this mechanism. Weight loss may also improve ED through other mechanisms, including decreased inflammation, increased testosterone, and improved mood and self-esteem. In the Look AHEAD (Action for Health in Diabetes) trial [73], cardioregulatory fitness was found to be protective against ED among the 373 diabetic men aged 45–75 years. In particular, fitness was measured by a symptom-limited graded-treadmill exercise test to the point of voluntary exhaustion; after adjusting for age and other covariables, men with greater fitness had a 39% lower risk of ED.

Another way to improve sexual activity is to improve erectile function. It is important to obtain good glycaemic control and to stop smoking because both result in poor glycaemic control [74,75], while a smoking habit is strongly associated with ED [76].

Prescription drugs and over-the-counter medications should also be checked out as possible contributors to ED. Effort should be made to avoid or to find substitutes for drugs that have negative impacts on sexual function. In particular, it has been shown that treatment with angiotensin receptor blockers may be associated with improvement in erectile function [77]. In contrast, some drugs, such as diuretics and the older beta-blockers, should be avoided for treating hypertension [76]. These drugs should only be used when specifically indicated, such as for coronary heart disease, heart failure or arrhythmias. However, it is worth noting that some of the recently developed beta-blockers, such as nebivolol, could have a positive effect on sexual function [78] due to improvement of the endothelial function of penile vessels.

While hypogonadism and ED have emerged as predictors of CVD that may respond to the lifestyle changes commonly recommended for patients with diabetes and the metabolic syndrome, the literature on whether or not treatment with testosterone supplementation affects outcomes beyond well-being and sexual function is still emerging [57,79]. Despite the well-known link, the role of testosterone replacement therapy in type 2 diabetes has not been completely clarified. In addition, relationship counselling and psychiatric medications may be useful for treating anxiety and depression.
Fig. 2. Management algorithm of erectile dysfunction (ED) in diabetes patients.

**2.3.3. First-line therapy: the phosphodiesterase-5 inhibitors**

Selective PDE5 inhibitors (sildenafil, vardenafil and tadalafil) represent the first-choice treatment strategy for ED. They have favourable safety profiles, and the common side-effects include headache, flushing, dyspepsia, nasal congestion, abnormal vision and diarrhoea. These drugs prevent the breakdown of cGMP and enhance erectile function. They are not initiators of erection and require sexual stimulation for an erection to occur. The proportion of men with diabetes who experienced improvement of ED with the administration of PDE5 inhibitors ranged from 57% to 74% in two pivotal trials [80,81]. In addition, a recent Cochrane review concluded that PDE5 inhibitors improved ED in diabetic men [82].

Nevertheless, the response to such treatment has been lower in diabetic than in non-diabetic subjects [83,84], as was also confirmed by a specific meta-analysis [85]. Indeed, treatment with sildenafil can improve sexual function in about 63% of type 2 diabetes patients, but the response rate was significantly higher (83%) in non-diabetic subjects [85].

The lower response rate observed in diabetic patients may be explained by the fact that type 2 diabetes, obesity and the metabolic syndrome are often characterized by hypogonadotropic hypogonadism. For this reason, free testosterone levels should be measured in patients who fail to respond to treatment with PDE5 inhibitors; if the levels are low, then testosterone replacement therapy should be considered [76].

Despite the differences among the available PDE5 inhibitors in terms of pharmacokinetics and pharmacodynamics, their clinical effects in diabetic ED patients are similar. However, there is insufficient information to single out the superior efficacy of any one of the currently available PDE5 inhibitors for diabetic ED patients. The choice of PDE5 inhibitor depends on the frequency of intercourse (occasional use or regular therapy, three to four times weekly) and the patient’s personal experience with the agent. Table 1 summarizes the main results of double-blind randomized studies for the effects of PDE5 inhibitors on erectile function in diabetic patients. Sildenafil was the first oral selective PDE5 inhibitor used in 1998 for diabetic patients with ED, and was found to improve erections in 52% of patients treated with
Table 1
Efficacy of phosphodiesterase type-5 (PDE5) inhibitors in the treatment of erectile dysfunction in diabetes patients.

<table>
<thead>
<tr>
<th>Authors [reference]</th>
<th>Number of patients</th>
<th>Type of diabetes</th>
<th>PDE5 and posology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stuckey et al., 2003 [116]</td>
<td>188 (placebo = 93)</td>
<td>1</td>
<td>Sildenafil 25–100 mg</td>
<td>IIEF: Q3: 3.61 vs 2.71, P &lt; 0.001 Q4: 3.25 vs 2.19, P &lt; 0.001</td>
</tr>
<tr>
<td>Rendell et al., 1999 [81]</td>
<td>268 (placebo = 132)</td>
<td>1 and 2</td>
<td>Sildenafil 25–100 mg</td>
<td>IIEF: Q3: 3.2 vs 2.0, P &lt; 0.001 Q4: 2.9 vs 1.6, P &lt; 0.001</td>
</tr>
<tr>
<td>Safarinejad et al., 2004 [117]</td>
<td>262 (placebo = 128)</td>
<td>1 and 2</td>
<td>Sildenafil 10 mg</td>
<td>IIEF: Q3: 2.8 vs 2.2, P &lt; 0.002 Q4: 2.9 vs 2.0, P &lt; 0.002</td>
</tr>
<tr>
<td>Boulton et al., 2001 [118]</td>
<td>219 (placebo = 109)</td>
<td>2</td>
<td>Sildenafil 25–100 mg</td>
<td>IIEF: Q3: 3.42 vs 1.86, P &lt; 0.0001 Q4: 3.35 vs 1.84, P &lt; 0.0001</td>
</tr>
<tr>
<td>Goldstein et al., 2003 [80]</td>
<td>430 (placebo = 140)</td>
<td>1 and 2</td>
<td>Vardenafil 10–20 mg</td>
<td>IIEF: 5.9–10.8 vs 1.4, P &lt; 0.0001 SEP: Q2: 61–64% vs 36%, P &lt; 0.0001 Q3: 49–54% vs 23%, P &lt; 0.0001</td>
</tr>
<tr>
<td>Ishii et al., 2006 [88]</td>
<td>783 (placebo = 111)</td>
<td>2</td>
<td>Vardenafil 10–20 mg</td>
<td>IIEF: 13.9–22.9 vs 16.3, P &lt; 0.0001</td>
</tr>
<tr>
<td>Ziegler et al., 2006 [89]</td>
<td>302 (placebo = 149)</td>
<td>1</td>
<td>Vardenafil 5–20 mg</td>
<td>SEP: Q2 and Q3: P &lt; 0.0001</td>
</tr>
<tr>
<td>Saenz de Tejada et al., 2002 [119]</td>
<td>145 (placebo = 71)</td>
<td>1 and 2</td>
<td>Tadalafil 10–20 mg</td>
<td>IIEF: 6.4–7.3 vs 0.1, P &lt; 0.001 SEP: Q2: 22% vs no response, P &lt; 0.001 Q3: 28–29% vs 1.9%, P &lt; 0.001</td>
</tr>
<tr>
<td>Hatziichristou et al., 2008 [120]</td>
<td>298 (placebo = 100)</td>
<td>1 and 2</td>
<td>Tadalafil 2.5 or 5 mg daily</td>
<td>IIEF: 4.8–4.5 vs 1.3, P &lt; 0.005 SEP: Q2: 20.5–28.9% vs 5.3%, P &lt; 0.005 Q3: 25.9–25% vs 8.2%, P &lt; 0.005</td>
</tr>
</tbody>
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IIEF: International Index of Erectile Function; SEP: Sexual Encounter Profile Questionnaire.

50 mg of sildenafil compared with 10% of the control group [86]. Furthermore, it has been suggested that the daily use of sildenafil might enhance endothelial function and improve penile rigidity in some diabetic ED patients [87].

A prospective multicentre, double-blind, placebo-controlled, fixed-dose, parallel-group phase III trial of vardenafil showed a dose-dependent (P = 0.02) improvement in erections, according to a global-assessment questionnaire, for 57% and 72% of diabetic men (including both type 1 and type 2) with ED taking vardenafil at 10 mg and 20 mg doses, respectively; this was in contrast to a 13% improvement for men taking the placebo (P < 0.0001) [80]. Ishii et al. [88] also found an incremental clinical benefit with the higher dose (vardenafil 20 mg) in diabetic ED patients. Yet another multicentre, double-blind, placebo-controlled clinical trial of vardenafil in type 1 diabetes patients with ED demonstrated a significantly improved mean success rate on the Sexual Encounter Profile Q2 and Q3 compared with baseline and placebo at 4, 8 and 12 weeks (P < 0.0001). Vardenafil treatment also significantly improved the erectile-function domain score (P < 0.0001) of the International Index of Erectile Function (IIEF) Questionnaire compared with a placebo [89].

Tadalafil, a long-acting PDE5 inhibitor, is also effective and well tolerated. Patients with diabetic ED receiving tadalafil 20 mg experienced a mean improvement of 7.4 in their IIEF erectile-function domain score against baseline vs 0.9 with the placebo (P < 0.001), as well as an improvement in successful intercourse attempts (53% vs 22%, respectively) [90]. Tadalafil 20 mg, when taken on demand or three times a week, is effective and safe for diabetic men with ED [91].

2.3.3.1. Phosphodiesterase type-5 inhibitors for diabetes patients with coronary artery disease. CAD patients can take selective PDE5 inhibitors to treat ED. However, it is important to remember that PDE5 inhibitors cannot be used in patients using nitrates, as severe hypotension may then occur [70,92]. In addition, PDE5 inhibitors should not be used by patients taking alpha-blockers without first taking some specific precautions [76]. It is also important to bear in mind that silent CAD is particularly frequent in diabetic patients.

2.3.3.2. Cardioprotective effects of the phosphodiesterase type-5 inhibitors. In patients with stable CAD, PDE5 inhibitors can have positive effects on the cardiovascular prognosis. Indeed, a study has shown that CAD patients taking these drugs may experience a reduction in major adverse cardiovascular events [36]. These drugs were designed to be anti-angina agents [83,84], but then proved able to improve endothelial dysfunction. In addition, several recent studies have shown that PDE5 inhibitors can have cardioprotective effects [84,93–99]. Specifically, it has
been documented that PDE5 inhibitors can increase myocardial blood flow during workload [94], have preconditioning-like effects [95], reduce ischaemic cell death [96], increase the number of functional circulating angiogenic cells [97], dilate the epicardial coronary artery and inhibit platelet activation [98]. Thus, these studies demonstrate additional potential pathophysiological mechanisms through which PDE5 inhibitors might reduce cardiovascular events and death in addition to improving endothelial function. Indeed, the preclinical results and findings of the study by Gazzaruso et al. [36] suggest the need for a long-term, randomized, placebo-controlled trial of PDE5 inhibitors in patients with risk factors for CAD who may ultimately suffer major adverse cardiac events.

2.3.3.3. The new phosphodiesterase type-5 inhibitors. The new generation of PDE5 inhibitors, such as udenafil and mirodenafil, is promising. Udenafil was developed as a new drug for ED, and is now marketed in Korea and Great Britain. The advantages of udenafil include a long period of activity, rapid absorption, and mild adverse effects limited to flushing and headache. Udenafil has proved significantly effective for the treatment of ED, demonstrating a statistically significant improvement in erectile function in patients with diabetes. The incidence of adverse events is relatively low and well tolerated in such patients [100]. Mirodenafil, available in Korea, has also been shown to be effective [101]. The use of drugs with different pharmacological profiles may, it is hoped, lead to better sex-related responses in diabetic men with ED.

2.3.4. Second-line therapy
2.3.4.1. Intracavernosal injections of prostaglandins. Patients not responding to oral drugs may be offered intracavernous injections of alprostadil. Prostaglandin E1 (PGE1) stimulates adenylyl cyclase, thereby increasing levels of cyclic adenosine monophosphate (cAMP), which results in smooth muscle relaxation, vasodilatation and inhibition of platelet aggregation. Erection appears after 5 to 15 minutes and lasts for a period that depends on the dose injected. The patient should be enrolled in an office-based training programme (requiring one or two visits) to learn the correct injection procedure. The efficacy rate is approximately 70%, with reported sexual activity after 94% of injections, and satisfaction rates are high [102]. However, dropout rates of 41–68% have been reported, with most dropouts occurring within the first 2 to 3 months [103]. Complications with intracavernous alprostadil include penile pain (50% of patients after 11% of injections), prolonged erections (5%), priapism (1%) and fibrosis (2%) [104].

Drug combinations such as alprostadil plus papaverine, a non-specific PDE inhibitor resulting in increased levels of cAMP and/or cGMP, and inhibition of calcium channels and angiotensin-II secretion, and alprostadil plus phenolamine, a competitive antagonist of α-1 and α-2 adrenoreceptors, may increase efficacy by up to 90%.

2.3.4.2. Intraurethral prostaglandin suppositories. PGE1 is also available as an intraurethral suppository. The proposed mechanism of action involves the absorption of intraurethral alprostadil by the urethra and its subsequent transport to the corpus cavernosum, where it leads to vasodilatation and relaxes smooth muscle through its interaction with a prostacyclin receptor. It is less invasive and easier to use than an intracavernosal injection, but it may adversely affect sexual spontaneity. The efficacy of alprostadil is similar regardless of the aetiology of ED [105].

2.3.4.3. Vacuum constriction devices (VCDs). A VCD applies negative pressure on the penis to draw venous blood into the penis that is then retained by the application of a visible constricting band at the base of the penis. This method appears to be more acceptable to older patients [106]. There are few recognized complications, and there are low-cost treatment options for selected diabetic ED patients. It was reported that VCDs achieved satisfactory erections in more than 70% of diabetic men [107]. Problems with VCDs include pain from the constriction ring, lack of spontaneity, decrease in the quality of orgasm and ejaculatory discomfort. In addition, up to 30% of patients discontinue use as the result of inadequate rigidity, penile pain, failure to ejaculate and the appearance of the penis while using the device [107,108]. Other disadvantages include lack of spontaneity and, in a minority of cases, the partner deemed it an unacceptable method.

2.3.4.4. Yohimbine. Yohimbine, an alpha-adrenergic receptor antagonist, is recommended in a dose of 5–10 mg three times a day. This agent is considered to have modest efficacy in treating ED, with positive response rates of 30% in diabetic cases [109]. Side-effects, such as anxiety and headache, have been reported to be infrequent and mild.

2.3.5. Third-line therapy: penile implants

When pharmacotherapy fails, surgical implantation of a penile prosthesis may be considered. Prostheses are either malleable (semi-rigid) or inflatable (two- or three-piece). Penile implants provide a predictable and reliable erection, and have the highest satisfaction rate among both patients and their partners of all the available treatments for waning erections [120–123].

The two main complications associated with penile prosthesis implantation are mechanical failure (<5% after a 5-year follow-up with the currently available three-piece prostheses) and infection. However, around 10 years ago, American Medical Systems introduced a three-piece inflatable penile implant (InhibiZone, AMS 700TM) impregnated with the antibiotics minocycline and rifampin. Since then, there has been a dramatic reduction in infection rates among those with an antibiotic-impregnated penile implant in the general population of first-time impregnated penile-implant recipients; currently, the infection rate is 1% [110]. For non-impregnated implants, the infection risk rate is 2.5% in this population [110,111]. Some research has indicated that diabetics have an increased risk of infection vs non-diabetics, but other studies have indicated no differences in infection rates [111–115].
3. Conclusion

ED is common in diabetes patients, but the pathogenesis of diabetic ED is multifactorial and complex. Endothelial dysfunction is considered the key mechanism of ED development in diabetic patients. In addition, ED is strongly associated with the future occurrence of cardiovascular events and appears to be a strong marker of silent CAD. Diabetic ED can be safely and effectively treated with PDE5 inhibitors. However, before resuming sexual activity, myocardial ischaemia has to be excluded. Given the evidence that PDE5 inhibitors can improve endothelial function and might even have a primary cardioprotective effect, the time has come to study these agents systematically as potential therapies for the prevention of adverse cardiac events in patients with vascular risk factors.

At present, there is no treatment specifically designed for diabetic ED, but the appropriate use of insulin to control blood glucose should be considered the first step. Also, combination therapy may achieve the best treatment results. Treating ED among diabetics is a top priority.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


