Paolo Pozzilli (Orcid ID: 0000-0001-5090-636X)

Erectile dysfunction and diabetes: a melting pot of circumstances and treatments

Short running title: Erectile dysfunction and diabetes

Authors: Giuseppe Defeudis*[1], Rossella Mazzilli*[2], Marta Tenuta[3], Giovanni Rossini[1], Virginia Zamponi[2], Soraya Olana[2], Antongiulio Faggiano[2], Paolo Pozzilli[1], Andrea M. Isidori[3], Daniele Gianfrilli[3]

[1]Unit of Endocrinology and Diabetes, Department of Medicine, University Campus Bio-Medico di Roma, Via Alvaro del Portillo 21, 00128 Rome, Italy

[2]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

[3]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

* Giuseppe Defeudis and Rossella Mazzilli should be considered joint first author

Corresponding author:

Dr Giuseppe Defeudis

g.defeudis@unicampus.it

Unit of Endocrinology and Diabetes, Department of Medicine, University Campus Bio-Medico di Roma, Via Alvaro del Portillo 21, 00128 Rome, Italy

Tel +39 06 225419184

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Abstract

Diabetes mellitus (DM), a chronic metabolic disease characterised by elevated levels of blood glucose, is among the most common chronic diseases. The incidence and prevalence of DM have been increasing over the years. The complications of DM represent a serious health problem. The long-term complications include macroangiopathy, microangiopathy and neuropathy as well as sexual dysfunction (SD) in both men and women. Erectile dysfunction (ED) has been considered the most important SD in men with DM. The prevalence of ED is approximately 3.5-fold higher in men with DM than in those without DM.

Common risk factors for the development of DM and its complications include sedentary lifestyle, overweight/obesity and increased caloric consumption. Although lifestyle changes may help improve sexual function, specific treatments are often needed.

This study aimed to review the definition and prevalence of DM and ED, the impact of DM complications and DM treatment on ED and current and emerging treatments and novel approaches for the treatment of ED in patients with DM.

Keywords: erectile dysfunction, diabetes, diabetes treatment, diabetes complications, PDE5 inhibitors, hypogonadism.

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases and is characterised by impaired carbohydrate metabolism. The incidence and prevalence of DM have increased over the years, with its complications representing a serious health problem. The long-term complications of DM include macroangiopathy, microangiopathy and neuropathy. DM is also an important cause of sexual dysfunction (SD) in both men and women, with erectile dysfunction (ED) considered the most important SD in men with DM.

A sedentary lifestyle, overweight/obesity and increased caloric consumption have been identified as common risk factors for the development of DM and DM complications. Although lifestyle changes may help improve sexual function, specific treatments are often needed.

This review therefore focuses on determining (i) the definition and prevalence of DM and ED, (ii) the impact of DM complications and other cofactors on ED and (iii) current and emerging treatments and novel approaches for the treatment of ED in patients with DM.

Epidemiology

The incidence rate of ED is estimated at 25–30 cases per thousand person years, with approximately 20%–30% of adult men having at least one SD.[1] Certainly, age is an important risk factor for SD, and the prevalence of SD increases with age, ranging from 1%–10% in men aged <40 years to 50%–100% in men aged >70 years.[2,3]

Men with DM are at a significantly higher risk for ED than those without DM. In line with this, Corona et al. reported a 19.4%, 15.4%, 10.4% and 21.6% prevalence of mild, mild-to-moderate, moderate and severe ED in men with DM, respectively.[4] The severity of ED is highly dependent on the type and duration of DM, type of treatment and comorbidities.[5-7] A study conducted by Fedele et al. on a large population of men with DM showed a 26% and 37% prevalence of ED among those with type 1 DM (T1DM) and type 2 DM (T2DM), respectively.[6] Similarly, a recent meta-analysis showed that the overall prevalence rate of ED in patients with DM was 52.5% (95% confidence interval [CI], 48.8–56.2), with prevalence rates of 37.5% and 66.3% in those with T1DM and T2DM, respectively.[8] Accordingly, patients with DM had an approximately 3.5-fold higher prevalence of ED than those without DM.

The 'complicated role' of complications and cofactors in the pathophysiology of ED in DM

ED has a very complex aetiology which can involve numerous unmodifiable and modifiable factors, which are often present at the same time and usually can influence each other. Common risk factors include, besides DM, age, dyslipidaemia, hypertension, cardiovascular disease, obesity, metabolic syndrome (MetS), lack of exercise, and smoking[9-11]. Vasculogenic factors are the most common and are both due to arterial inflow or venous outflow disorders[9]. Other factors include low testosterone levels, neurogenic and iatrogenic factors (related to a medical or surgical treatment)[12,13]. Moreover, also a psychological component is involved, thus complicating the clinical picture and worsening the quality of life[14].

It is therefore clear how many risk factors between ED and DM are in common. As hyperglycaemia is associated with increased oxidative stress, and the hyper-production of reactive oxygen species (ROS), in DM a cascade of events occurs: reduced NO, increased prothrombotic factors such as tissue factor and plasminogen activator inhibitor-1, an increase in endothelin-1, with subsequent thrombosis and vasoconstriction, as well as an increase in nuclear factor kappaB and activation protein 1 with subsequent inflammation, culminating in ED[15]. In fact, the aetiology of ED in diabetic subjects could be described as a "diabetic erectile dysfunction wall".

The management of DM is exceedingly complex because of its acute and long-term complications and several comorbidities. Thus, the incidence rates of ED in patients with DM increase with the number and severity of complications and comorbidities[16]. Therefore, a complete andrological evaluation cannot overlook the complex management of DM. Similarly, the framework of patients with DM cannot be complete without careful andrological evaluation given that ED symptoms also offer a great opportunity for the early diagnosis and better management of DM complications.

The main complications and comorbidities related to ED are schematically presented in **Fig. 1** and are discussed below.[17]

Complications:

Cardiovascular events

Cardiovascular disease (CVD) is the main cause of mortality and morbidity in patients with DM.[18] CVD is strictly dependent on atherosclerotic complications, which are also responsible for ED.

The direct correlation between ED and CVD has been widely confirmed in the literature.[9,19-23] Recent real-world observational data have shown that patients with ED have a higher prevalence of CVD and DM than patients without ED in every age group, beginning from 30 years of age, peaking between at 60–69 years, and persisting throughout life.[24] Moreover, ED can precede the onset of coronary artery disease (CAD) by 2–5 years, providing a great opportunity for the early diagnosis of silent CAD and stroke,[25] particularly in patients aged <60 years.[26] Atherosclerotic complications affect smaller arteries, such as those in cavernous areas, before affecting the larger ones (e.g. coronary, femoral and carotid arteries). The difference between vascular and chronological age (determined from the SCORE project algorithm[27]) can be a predictor of major adverse cardiovascular events and has been correlated with poor penile colour Doppler ultrasound parameters, even in patients referred for ED without a personal history of cardiovascular events, representing an inexpensive and safe surrogate marker of penile and systemic arterial damage.[28,29]

The association between ED and CVD carries considerable importance in patients with DM.[30] Despite several algorithms enabling cardiovascular and metabolic risk stratification in patients with DM,[31] a large number of silent CAD can be overlooked. Identification of ED can therefore represent an additional tool in the evaluation of the latter category of patients, especially younger patients.[32,33] ED should be considered an effective zero-cost predictor of CVD and requires further diagnostic investigation and aggressive risk-decreasing therapy, especially in young men.[34]

Nephropathy

Diabetic nephropathy, which occurs in 20%–40% of patients with DM, is dependent on increased arteriolar resistance and, therefore, glomerular pressure and hyperfiltration. A strong correlation between albuminuria and ED has been reported.[35,36] The activation of the renin–angiotensin system increases the production of pro-inflammatory and pro-fibrotic molecules (endothelin-1 and urotensin II), which further increases arteriolar resistance and simultaneously reduces nitric oxide (NO) production due to changes in the renal biosynthesis of L-arginine (a substrate of NO) and increased production of asymmetric dimethylarginine, an endogenous inhibitor of NO synthase.[37]

Erectile function is therefore common in patients with chronic kidney disease (CKD), with the severity of the former being directly proportional to that of the latter.[38] Besides endothelial and vascular damage, other mechanisms are involved in the association between ED and diabetic nephropathy, especially in the advanced stages of CKD and end-stage renal disease, regardless of DM.[39,40] First, evidence has shown that uremic state is associated with peripheral neuropathy (also at the penile level) and hypothalamic–pituitary–gonadal axis derangement,[41] which results is hypergonadotropic hypogonadism, suggestive of primary testicular damage.[42] Consequently, testosterone levels decrease significantly as CKD progresses.[43] Previous studies on testicular biopsies in patients with kidney failure have shown Leydig cell abnormalities, particularly with regard to number and morphology[44] but not hypertrophy or hyperplasia, suggesting LH resistance rather than a cytotoxic effect of uraemia. In this regard, in vitro findings revealed LH receptor blockage in uremic serum.[45] LH levels are only modestly increased during such conditions, suggesting a reduced central response to decreased testosterone levels related to a uraemic state. Patients undergoing dialysis, however, deserve a separate discussion. In such conditions, reduction in testosterone levels may depend on histological changes in the gonads induced by substances used during dialysis or from the loss of most steroid precursors during dialysis procedures.[46] Second, SD could also depend on hyperprolactinaemia, a very common finding in end-stage renal disease or secondary hyperparathyroidism.[47] In fact, partial inhibition of parathyroid hormone release following calcitriol administration may increase testosterone levels and improve sexual function.[48] Finally, autonomic nervous system dysfunction, secondary to uremic toxins (urea, creatinine, parathyroid hormone, myoinositol, β2-microglobulin and asymmetric dimethylarginine), can negatively affect erectile function.[49]

Neuropathy

Diabetic neuropathy is another important microvascular complication. Ischaemia, Advanced glycation end products (AGE) and free radical formation can impair axonal transport and nerve conduction, causing segmental demyelination.[50] Diabetic neuropathy is also involved in ED, as reported by many large studies.[49-54]

Both peripheral and autonomic neuropathy contribute to ED. Peripheral neuropathy is responsible for the impairment of sensory impulses from the penis to the reflexogenic erectile centre and motor impulses to the pelvic floor muscles, which leads to a reduction in the contractile force of the bulbocavernosus and

ischiocavernosus muscles and, therefore, venous outflow from the corpora cavernosa.[51,52] In addition, as previously reported, peripheral neuropathy worsens considerably in uremic patients with renal failure.[41] On the other hand, autonomic neuropathy is characterised by a decrease or absence of parasympathetic activity, which is necessary for relaxation of the corpora cavernosa smooth muscle.[53] Moreover, autonomic postganglionic parasympathetic nerves produce neuronal Nitric Oxide Synthase. The neuronal integrity of the cavernous nerve is therefore crucial for penile erection given that the nitric oxide secreted from the nerve terminal is responsible for initiating the erectile mechanism, which is subsequently maintained by eNOS and Akt activation,[54] indicating that diabetic neuropathy compromises both the initiation and maintenance of erection.

Comorbidities:

ED and DM share common risk factors and are associated with diseases causing endothelial impairment, such as hypertension, dyslipidaemia, obesity and MetS. Other comorbidities include hypogonadism, urological disease, obstructive sleep apnoea and depression. ED can therefore be identified as an independent risk factor apart from those already mentioned in patients with DM.

Hypertension

Hypertension is among the most common comorbidities in patients with diabetes and one of the major risk factors for CAD, CKD and consequently, premature death.[55-59] High blood pressure (BP) can influence erection mainly because of the resulting penile arterial dysfunction,[60] including arterial stenosis and smooth muscle tissue hypertrophy, which reduce blood flow and cause endothelial damage, thereby reducing NO production.[61] Several trials have confirmed the strong association between ED and hypertension.[3,62-66] Results from the SPRINT trial showed that ED was very common in middle-aged and older men with hypertension, affecting 59.9% of the patients. The authors, however, concluded that this percentage may be higher considering that patients who already received phosphodiesterase (PDE) inhibitor treatment were also included in the study. The same study also showed that systolic BP (SBP) was inversely correlated with IIEF-5 score, even after adjusting for several covariates.[67] This correlation was also reported in a recent study on 692 patients with T1DM, which showed that the risk of ED increased significantly for each 10-mmHg increase in SBP above

normal values, even after adjusting for age, cigarette smoking and HbA1c levels.[68] Accordingly, significant reductions in both SBP and diastolic BP (DBP) have been shown to significantly improve erectile function in patients treated for coronary heart disease.[69] This improvement was even greater after excluding patients with DM, indicating that optimal BP control may not be sufficient in patients with DM.

The relationship between hypertension and ED is difficult to establish given the coexistence of many risk factors in the majority of men with ED. In contrast with previous reports, some studies showed that high BP was not correlated with an increased risk of ED[70] and that BP control did not result in better outcomes of erectile function[71] even after 6 years of follow-up.[72]

In fact, a number of pharmacological treatments for hypertension may adversely affect sexual and erectile function, further complicating the interpretation of the results of many studies. Delineating the effects of a single drug is considerably difficult given the many interrelated factors, overlapping pathologies and multiple medications associated with ED. Evidence suggests that diuretics and β-blockers (with the exception of nebivolol) are mainly associated with ED. A study showed that β-blockers act both centrally (i.e. reduce testosterone levels) and peripherally (i.e. act on penile vascular smooth muscle cells and cause vasoconstriction).[73] The safety of nebivolol is instead related to its vasodilating properties depending on endothelial release of NO.[74-76] Thiazide diuretics and aldosterone receptor antagonists (spironolactone and eplerenone) have also been associated with ED, the former probably due to a direct effect on penile vascular smooth muscles and the latter to its anti-androgen effect due to competitive binding with androgen receptors.[77-79] On the other hand, calcium channel blockers have been associated with a neutral effect on erectile function, and angiotensin-converting enzyme inhibitors and mostly angiotensin receptor blockers seem to even improve it given that they block the vasoconstrictive action of angiotensin-II.[80-83] Given the aforementioned data, clinicians should customise anti-hypertensive therapies, particularly in patients with DM, who are at high risk for ED, considering angiotensin receptor blockers as their first choice, followed by angiotensin-converting enzyme inhibitors and calcium channel blockers, with nebivolol as the preferred β-blocker therapy when needed.

Dyslipidaemia

Considering the significant increase in atherogenic risk caused by dyslipidaemia, the significant contribution of vascular mechanisms to ED is unsurprising.[84] Dyslipidaemia is an independent risk factor for ED in patients with DM,[85] and patients with both DM and ED have a 2.3-fold higher risk for dyslipidaemia.[69,86] High LDL levels, low HDL levels,[87] and hypertriglyceridemia[88] have been linked to ED[89] despite the difficulty of evaluating the isolated effects of a single lipid class. Moreover, low serum testosterone levels have also been associated with dyslipidaemia, with the most recent evidence showing that testosterone replacement therapy (TRT) can have some beneficial effects on lipid metabolism in hypogonadal patients with T2DM.[90,91]

Finally, statins are usually prescribed among medications related to ED given previous findings showing an association between statin use and low testosterone levels.[92] However, recent meta-analyses have found no evidence that statins impair erectile functions.[93-95]

Obesity and MetS

T2DM has been strongly associated with obesity, leading to the coining of the term 'diabesity',[96] despite the increasing prevalence of overweight and obesity among patients with T1DM.[97]

The accumulation of visceral adipose tissue has been associated with MetS and cardiovascular risk. Obesity, MetS and T2DM have been associated with chronic low-grade inflammation: visceral adipose tissue promotes insulin resistance and consequent hyperglycaemia and is able to release inflammatory cytokines (TNF-α and IL-6), promote the endothelial expression of chemokines (IL-1) and adhesion molecules as well as inhibit anti-atherogenic factors (adiponectin), representing the starting condition of the inflammatory state, oxidative stress, endothelial dysfunction and therefore CVD.[98] For these reasons, ED has been frequently associated with obesity but even more with metabolic diseases.[99-102] According to Lotti et al., patients with metabolically healthy obesity did not have poorer erectile functions than controls, as opposed to those with metabolically complicated obesity,[103] suggesting that metabolic risk factors represent the main cause of impairments in erectile function.

Moreover, hypogonadism represents another crucial element of this complicated vicious circle. Visceral obesity and MetS are considered among the main determinants of low testosterone levels, with low testosterone levels simultaneously being an independent risk factor for obesity, MetS and T2DM, thereby reinforcing the cycle.[104]

According to current clinical evidence, ED and MetS in patients with obesity mainly depend on arterial dysfunction and reduced testosterone levels.[105] Therefore, comprehensive metabolic assessment and routine hormonal screening for male hypogonadism should be recommended in male patients with obesity with concomitant DM and ED.[31,106]

Weight loss should be the first-line therapeutic approach for improving erectile function in obese men with DM.[107] Most studies that examined the impact of lifestyle modification, diet and exercise on weight loss showed an inverse correlation between body mass index (BMI) and testosterone levels, in addition to an improvement in glycaemic control and metabolic parameters.[108,109] Bariatric surgery has been shown to be more effective than nonsurgical options for weight loss in individuals with severe obesity.[110] According to a prospective long-term randomised controlled trial (RCT) that compared surgical and nonsurgical treatments for weight loss and their subsequent impact on sexual hormones and erectile function, the former resulted in higher testosterone levels and improved erectile function.[111]

Data from many single-centre[112-115] and multi-centre[116,117] high-quality trials and meta-analyses[90] have highlighted the beneficial effects of TRT in patients with T2DM, obesity, MetS and ED. However, despite the encouraging results, the sole presence of obesity is not enough to start TRT according to the Endocrine Society practice guidelines for obesity. Nonetheless, TRT can be considered in individual cases who cannot achieve weight loss using conventional therapeutic approaches.[107]

Hypogonadism

ED is one of the first symptoms of hypogonadism because testosterone modulates nearly every step of erectile function[12] Considering the moderate prevalence of hypogonadism in patients with T1DM relative to those with T2DM,[118] hyperglycaemia in the absence of insulin resistance may not be enough to cause inhibition of the axis. Nevertheless, the association among hypogonadism, obesity, MetS, insulin resistance and T2DM is widely recognised and consists of a complicated vicious circle, in which obesity is a major confounder, as previously reported.[119] Initially, patients with T2DM, obesity and MetS could present with hypogonadism, with low testosterone levels also being associated with insulin resistance, further aggravating glycaemic

control, favouring the uptake of free fatty acids and proliferation of adipocytes and therefore promoting adiposity.

As reported in several cross-sectional studies,[120-123] up to 40% of men with T2DM exhibit low testosterone levels, with more than 90% experiencing ED.[124] Moreover, a study reported an inverse correlation between ED severity and testosteronelevels.[125] In the majority of patients with DM, low testosterone levels have been associated with inappropriately low gonadotropin levels, suggesting functional secondary hypogonadism (or late-onset hypogonadism). This could be related to both insulin resistance[126] and the negative feedback exerted by increased estradiol due to the aromatase activity of visceral fat.[127] Sex hormone-binding globulin (SHBG) levels are usually low in patients with DM and are inversely correlated with HbA1c levels. Low SHBG levels have been associated with an increased risk for the development of T2DM.[128] Current guidelines suggest hormone profile dosage in only patients with DM who have symptoms and signs of testosterone deficiency,[31,106] including total testosterone, LH, SHBG and free testosterone (measured directly or calculated using total testosterone, SHBG and albumin concentrations).[129]

In fact, there is no consensus regarding the beneficial effects of TRT on glycaemic control in patients with T2DM. Thus far, conflicting results have been reported, with some studies reporting beneficial effects of TRT on insulin sensitivity or HbA1c reduction[116,120,130-132] and others not.[117,121,133,134]

Given the lack of evidence, the Endocrine Society clinical practice guideline does not recommend TRT for improving glycaemic control. Nevertheless, it is strongly recommended to provide similar treatment for ED in hypogonadal men with and without T2DM.[106] Other beneficial effects of TRT include improvements in well-being, muscle mass and strength and bone density. However, the 2020 American Diabetes Association guidelines still highlight the need to consider the risk of increased cardiovascular events in older men with hypogonadism receiving TRT.[31] According to the recent evidences[106,135], however, there is no consistent evidence that testosterone supplementation increases the cardiovascular risk in hypogonadal men. However, most larger studies have included retrospective cohorts, prospective studies have been underpowered and meta-analyses have shown no significant associations. As such, TRT cannot be established as a causative factor for cardiovascular events.[136] Nonetheless, long-term data on the impact of untreated hypogonadism on mortality have also been lacking considering that low testosterone levels are a marker of cardiovascular risk.[137] In conclusion, current recommendations lean toward an individualised prescription of TRT after careful patient

evaluation and explicit discussions on the potential risks and benefits, even among patients with DM. Furthermore, such patients should always be encouraged to undertake lifestyle modifications (reduced caloric intake, healthy diet, increased daily physical activity, smoking cessation and reduced alcohol consumption) before considering TRT.[138]

Urologic comorbidities

Urologic comorbidities can occur in both T1DM and T2DM. The primary reason for such comorbidities is urogenital tract infections (UTI), which have higher incidence rates in patients with DM (increased urinary glucose excretion, greater adherence of bacteria to the uroepithelium, chronic neurologic bladder dysfunction and weakened immune responses). Furthermore, sodium glucose transporter 2 (SGLT2) inhibitors can slightly increase the risk of UTI, despite recent meta-analyses suggesting no increased risk of severe bacterial infections.[139,140] Male patients with DM (both T1DM and T2DM) have a threefold higher risk for asymptomatic bacteriuria and an increased risk of UTI recurrence,[141] balanitis, balanoposthitis and male accessory gland infection.[142] While *Escherichia coli* has been the most frequently observed pathogen, other unusual microorganisms can be found (e.g. *Klebsiella*, fungal infections, gram negative rods, enterococci, group B streptococci, *Pseudomonas* and *Proteus mirabilis*).[143] As such, early diagnosis of UTI is imperative to avoid complications such as emphysematous cystitis, pyelonephritis, renal failure and bacteraemia. Balanitis or balanoposthitis, which are very frequent in patients with DM, mainly depend on *Candida albicans*,[144] whereas male accessory gland infection often occurs in patients with DM with autonomic neuropathy.[145]

DM (T2DM more than T1DM) has also been associated with benign prostatic hyperplasia and lower urinary tract symptoms (LUTS).[146,147] Both hypoxia due to vascular damage and hyperinsulinaemia are in fact important stimuli for prostate growth.[148,149] In addition, increased HbA1c levels have been associated with further increased risk of overactive bladder urgency, urge urinary incontinence and nocturia.[150] Additionally, several studies have described a potential association between neuropathic complications and LUTS, also in T1DM.[151-153] Finally, Peyronie's disease (PD), a connective tissue disorder of the penis characterised by impaired deposition of collagen and formation of fibrous plaques that may cause penile deformity with consequent pain and discomfort during erections, must be considered.[154] DM has been identified as a risk factor for PD, with prevalence rates of DM among patients with PD ranging between 10% and 43%.[155,156]

In conclusion, urinary complications of DM have been associated with general discomfort and decreased quality of life, unfavourable psychological effects and possibly depression and psychiatric symptoms.[157] Recent findings have revealed that among men with DM, those with LUTS have a higher prevalence of ED than those without LUTS.[158,159]

Obstructive sleep apnoea syndrome

Obstructive sleep apnoea syndrome (OSAS) is commonly associated with T2DM.[160,161] Considering that obesity is a common risk factor for OSAS and T2DM, this relationship is not surprising and is mutual. OSAS is a widely recognised risk factor for the development of T2DM independent of obesity and other conventional risk factors. T2DM might also be a risk factor for OSAS, despite being relatively less explored in the literature.[162] ED is one of the clinical manifestations of OSAS, with both pathologies closely linked by endothelial dysfunction.[163-165] Sleep apnoea treatment, particularly continuous positive airway pressure, significantly improved the quality of life and IIEF score[166-169] but was less effective than PDE5 inhibitors (PDE5-is) such as sildenafil.[170,171] Continuous positive airway pressure, which can improve oxygenation of both the pituitary gland and corpus cavernosum,[172] can be considered as an additional treatment to optimise therapeutic outcomes in hypogonadal men. Weight loss also plays a major role and should always be encouraged. Evidence regarding OSAS treatment for glycaemic control is still conflicting, with uncontrolled studies reporting improvement but RCTs failing to show such benefits.[162]

Depression

Sexual function can result from not only autonomic processes but also emotional and cognitive processes. Therefore, the presence of depression is unequivocally associated with ED,[173,174] reduced libido and decreased frequency of intercourse. This association is considered bidirectional although it remains unclear whether depressive syndrome precedes ED or vice versa.[175] The incidence of depression is twofold higher in patients with DM than in patients without DM.[176,177] Moreover, the presence of ED (for all the organic reasons reported so far) can worsen a previously existing depressive state,[178] while the use of antidepressants can aggravate ED. According to a recent meta-analysis, the risk of ED in men with DM exhibiting depressive symptoms is more

than six-fold higher than that in men with DM without depressive symptoms, with overall crude and adjusted odds ratios of 6.40 and 3.08, respectively.[5]

Considering that depression in patients with DM can have a significant negative impact on self-care, glycaemic control, health outcomes and quality of life, this diagnosis should not be underestimated.[179] As such, routine assessment of depression and ED should be part of standard DM care, and psychosexual counselling should be considered as an effective tool for men with ED and DM.[180]

Other factors

Basic science research has expanded the knowledge on ED and identified several key molecular changes related to the pathogenesis of ED, including RhoA/Rho-associated protein kinase (ROCK) signalling pathway, renin-angiotensin system (RAS) and tumor necrosis factor-alpha (TNF-α).[181]

RhoA/ROCK signalling play a role in the maintaining of the flaccid penile state and its activity in the penis is a pathogenic factor contributing to ED development. To this regard, inhibition of RhoA-ROCK signalling seems to potentiate smooth-muscle relaxation in an NO-independent manner and could be considered a new therapeutic target for the treatment of ED[181-183].

Considering Angiotensin II (Ang II), which is the primary effector of the RAS, studies have demonstrated the presence and activity in the penis. In fact, elevated Ang II levels contribute to the development of ED both in humans and animal models[184] and might be considered as a promising therapeutic target for the treatment of ED[185].

Furthermore, clinical and experimental evidence demonstrates that cytokines, among which TNF-α, could play an important role in ED, particularly in the context of CVD. In fact, high levels of TNF-α were demonstrated in patients with ED[186].

Finally, endothelins are potent vasoconstrictor peptides that induce contraction of trabecular smooth muscles cells of the corpora cavernosa, mainly through transmembrane calcium flux, and calcium sensitisation by the Rho-Rho kinase pathway. Furthermore, elevated endothelin-1 levels are found in patients with DM and this

could increase the risk of ED; alternatively, alterations in endothelin receptor sensitivity, which can occur in conditions such as DM and hypertension, may enhance vasoconstrictor processes[187].

Effects of anti-diabetic drugs on male sexuality

Metformin

Several studies evaluating the effect of metformin in patients with DM and ED have mostly focused on the analysis of the four major mechanisms of arteriogenic ED[188]: (i) endothelium-dependent vasodilatory impairment, mediated by reduced bioavailability of nitric oxide and inducing vasoconstriction; (ii) elevation of sympathetic nerve activity, resulting in enhanced basal and myogenic tone within the corpus cavernosum; (iii) atherosclerotic luminal narrowing, which leads to reduced arterial flow to the penis[189] and (iv) hypogonadism.[190]

Regarding the first aspect, small arterioles of the penis dilate in response to vasoactive substances produced by endothelial cells, with NO considered the most important molecule.[191] This mechanism is called endothelium-dependent vasodilatation. In patients with insulin resistance, increased degradation and reduced nitric oxide synthesis can promote a state of NO deficiency.[192] The reduction in NO bioavailability induces vasoconstriction of the arteries, arterioles and sinusoids of the corpus cavernous.

Several animal studies and clinical trials have highlighted the possible positive effects of metformin on endothelium-dependent vasodilation. Vitale et al.[193] reported a correlation between the improvement of endothelium-dependent vasodilatation and the reduction of insulin resistance after administration of metformin (500 mg BID) for 3 months in a cohort of patients with MetS compared with that in a placebo group. Mather et al.[194] highlighted similar results after administering metformin (500 mg BID) in a cohort of patients with T2DM. In their study, a significant improvement in endothelium-dependent vasodilatation compared with that in the placebo group was observed. Nonetheless, both studies showed significant improvements only in endothelium-dependent vasodilatation, whereas no significant difference in the mechanism of endothelium-independent vasodilatation induced by vasoligating agents was observed.

According to Kaya et al., metformin played a protective role against endothelial dysfunction and may be useful for treating ED in patients with insulin resistance.[195]

Evidence has shown that patients with DM had a higher basal tone of the sympathetic system, as demonstrated by increased production of norepinephrine[196,197] and low frequency/high frequency ratio,[198,199] indicating relative sympathetic or parasympathetic dominance.[200] Several animal and human studies have highlighted the neuromodulatory effect of metformin. These studies, which focused on the effect on BP and heart rate parameters, suggested that metformin could attenuate excessive sympathetic nerve activity and is useful in improving erectile function.[201-203] Regarding hypertension and atherosclerosis, plaque formation in the penile arteries has been known to impair blood flow and promote ED.[204] Insulin resistance has been shown to induce hypertension through various mechanisms.[205] Therefore, metformin had been hypothesised to exert positive effects on BP reduction and ED. Although this effect has been demonstrated in animal models,[206,207] no clear consensus has yet been established in human clinical trials. However, recent studies showed that metformin had no benefit on BP in patients with DM.[208,209]

With regard to the reduction of testosterone levels,[190] metformin treatment for insulin resistance could be hypothesised to improve testosterone levels and consequently ED. There are limited and inconsistent data regarding the role of metformin in improving hypogonadism. In 2010, Casulari et al. reported that metformin in conjunction with lifestyle modifications had positive effects in patients with metabolic and hypogonadal syndrome. The authors concluded that treatment based on healthy diet and mild physical activity associated with metformin improved insulin sensitivity and increased total and free testosterone levels, regardless of the presence of hypogonadism.[210] A study by Hayder et al. found that metformin resulted in significantly lower testosterone levels, poorer sex drive and greater ED in patients with DM than in those receiving sulfonylurea and those without DM. These results could be explained by the inhibitory activity of metformin on cytochrome P450-C17a, which plays an important role in the synthesis of total testosterone and in the reduction of LH levels. Conversely, sulfonylureas can inhibit 11β-hydroxysteroid dehydrogenase type 1, reducing glucocorticoid biosynthesis and stimulating testosterone synthesis.[211]

Finally, the best evidence of metformin-induced (850 mg BID) ED improvement was shown by a double-blind pilot study on 30 men with insulin resistance and poor response to sildenafil (100 mg). The administration of metformin resulted in improved BMI and HOMA index and IIEF-5 scores.[212]

In conclusion, metformin should be considered for men with ED and MetS or DM who show poor response to PDE-5is.

Pioglitazone

Pioglitazone exerts its anti-diabetic effect by increasing insulin sensitivity via the activation of a nuclear receptor, the gamma isoform of peroxisome proliferator-activated receptor (PPARγ). Accordingly, PPARγ activation showed beneficial effects in several conditions, such as endothelial dysfunction, oxidative stress, metabolic disorders, atherosclerosis and inflammation, which are risk factors for ED.[213,214] In 2006, Kovanecz et al. conducted a study in rats with T2DM and demonstrated that pioglitazone (0.6 mg/kg) could prevent and improve veno-occlusive dysfunction in the long term, without a significant reduction in glycaemia, thereby demonstrating its vasoprotective role through a mechanism independent from glycaemic control.[215]

Studies conducted using animal models have also demonstrated the neuroprotective role of pioglitazone in rats undergoing bilateral cavernosal nerve crush injury.[216] In particular, Aliperti et al. examined the effects of pioglitazone on erectile function in a rat model undergoing prostatectomy and demonstrated that pioglitazone improved ED through the NO-mediated pathway with a dose-dependent mechanism.[217]

The only human trial investigating the effects of pioglitazone (30 mg once daily) on men with moderate-to-severe ED and poor response to sildenafil was conducted by Gholamine et al., who showed that the pioglitazone group had significantly better improvement in sildenafil responsiveness and erectile function determined using IIEF-5 (from moderate-severe ED to mild-moderate ED) compared with the placebo group. Furthermore, they found a correlation between improvement in ED and a significant reduction in total cholesterol levels.[218]

Glibenclamide

To the best of our knowledge, only one study has investigated the effects of glibenclamide on erectile function. Ruiz Rubio et al.[219] showed that the KATP channels play a key role in the relaxation of penile resistance arteries. The blockade of the KATP channels by glibenclamide (3 M) significantly reduced the relaxation of arterial muscle cells, resulting in reduced erectile function.

SGLT-2 inhibitors

SGLT2 inhibitors, the newest class of anti-hyperglycaemic agents, have been shown to promote urinary excretion of glucose by blocking its reabsorption in the renal proximal tubules.[220]

SGLT2 inhibitors have demonstrated unprecedented cardiorenal outcomes in large-scale clinical trials conducted on patients with T2DM who did and did not have established CVD, reducing the incidence of major cardiovascular events, total and cardiovascular mortality and hospitalisations for heart failure, as well as slowing down the progression of kidney disease.[221-226] Despite the considerable scientific interest in this class of drugs, no scientific studies have explored the impact of SGLT2 inhibitors on sexual function.

Only one trial has analysed the possible impact of SGLT2 on T2DM-associated ED in rats treated with empagliflozin or placebo for 4 weeks, followed by treatment with sildenafil. Erectile function was assessed by measuring intra-cavernous pressure during electrical stimulation of the cavernous nerve. The study demonstrated that empagliflozin could significantly improve erectile function in response to electrical stimulation of the cavernous nerve and sensitivity to PDE5-is. Such results could be attributable to improvements in metabolic parameters, enhanced neuronal terminal recruitment with increased NO synthesis and/or release and amelioration of NANC-mediated relaxation, thereby attenuating diabetic neuropathy.[227]

DPP4i and GLP1RA

There are limited studies on the effects of DPP4i and GLP1RA on male sexual function. Evidence from animal models suggests that DPP4i could improve erectile function in patients with T2DM, promoting vascular repair and endothelial function[228] and improving the effects of vasorelaxants mediated by vascular endothelial growth factor.[229] A randomised controlled study conducted on rats with induced DM and treated with liraglutide revealed the protective role of liraglutide on the endothelium of the corpora cavernosa due to its effect on the Akt/eNOS mechanism, with the consequent improvement of erectile function.[230]

Furthermore, Giagulli et al. evaluated the effect of liraglutide in obese, hypogonadal patients with T2DM who received metformin and testosterone replacement. The group with liraglutide showed greater benefits on erectile function as well as increased testosterone levels.[231]

Insulin

Insulin treatment improves erectile function in diabetes-induced rats. Yamanaka et al. demonstrated that rats treated with insulin showed higher intra-cavernous pressure than the control group, as well as reduced levels

of pro-apoptotic factors and increased levels of anti-apoptotic factors.[232] Similar results were obtained by Wang in 2014 and Choi in 2015.[233,234]

In 2004, Shirai et al. were the first to show that insulin treatment may restore erectile function through modulation of sex hormone receptor gene and protein expression in rats with DM, increasing the mRNA and protein expression levels of androgen receptor and oestrogen receptor-alpha.[235]

Treatment of ED in diabetes

Lifestyle modifications and glycaemic control

As widely reported thus far, sexual function is the result of the integrative responses of the vascular, neurologic, endocrine and psychologic systems. As such, ED treatment requires a wholistic approach, starting from correcting modifiable risk factors, promoting lifestyle changes and improving glycaemic control. In a systemic review and meta-analysis including 740 participants from four countries, lifestyle modifications aimed at decreasing cardiovascular risk demonstrated an improvement in sexual function.[236] Several RCTs analysing the effects of reduced caloric intake, better food quality with a Mediterranean diet and increased physical activity reported improvements in metabolic parameters, anthropometric measurements and sexual function.[237,238]

A weight loss of 5% from the initial weight has been the minimum recommended weight loss percentage for clinical benefit. Greater weight loss leads to even greater benefits in terms of reducing BP; improving LDL and HDL levels and insulin resistance and reducing the number of medications to control DM, hypertension, and dyslipidaemia.[239,240] As previously reported, weight loss is strongly recommended to improve erectile function considering that it can increase testosterone levels mainly by improving testicular function and reducing conversion of testosterone to β-estradiol via aromatase activity in the adipose tissue,[127] as well as increasing SHBG concentration as a consequence of reduced insulin levels.[241] While TRT can be considered in selected cases,[107] other strategies for weight loss include bariatric surgery[110] and some specific anti-diabetic drug classes, such as GLP1 receptor antagonist and SGLT2 inhibitors. However, evidence regarding the impact of these drugs on testosterone levels remains unclear.[242,243]

Physical exercise is strongly recommended for both patients with T1DM[244] and T2DM[245] given its contribution to weight loss, improved blood glucose control, reduced cardiovascular risk and improved well-being and sexual function.[246-248] While physical exercise may improve serum testosterone levels, high-intensity exercise can also be counterproductive.[249-251]

In some cases, however, intensive lifestyle intervention failed to produce significant improvement in erectile function,[238,252] suggesting that this approach would be most likely effective in cases of mild ED. Thus, most cases may require combined therapy.

PDE5is

PDE5is have been considered the first-line therapy for ED of any aetiology.[253] PDE5 inhibition increases cGMP levels in cavernosal tissues, leading to smooth muscle relaxation, increased arterial blood flow, venous constriction and erection.[254] Several clinical trials, however, have shown that this class of drugs had blunted efficacy in patients with DM.[255,256] The lower efficacy of PDE5is in this population can be attributed to the multifactorial nature of the disease. In patients with DM, macrovascular complications and impaired neurogenic and endothelium-dependent relaxation of penile arteries reduce blood supply to the penile arteries. Moreover, the concomitant use of different medications to treat diabetes-related comorbidities and the higher incidence of hypogonadism may contribute to the reduced effectiveness of PDE5is.[257] Several studies have also shown that alterations in both the structures and molecular pathways supporting erectile function lead to reduced nitric oxide levels and responsiveness, thereby decreasing cGMP concentration in penile tissues.[258,259] This often requires higher PDE5i doses or combined therapies to achieve satisfactory results.[259]

While four main PDE5is are available globally (sildenafil, tadalafil, vardenafil and avanafil), other agents, such as mirodenafil, udenafil and lodenafil, are available in certain countries.[260] Structural differences among these PDE5is result in differences in pharmacokinetics and dynamic properties, which translate to different durations of action and methods of administration.[261] Most PDE5is have a half-life ranging from 2 to 5 h, with a mean duration of action of 6–12 h and an onset of action of 30–60 min.[262] In addition to on-demand use given their longer half-life and duration of therapeutic effect, tadalafil and udenafil are suitable for low-dose daily administration,[263] and this regimen has been approved for ED treatment.[262, 264] Daily tadalafil and udenafil use, however, did not show a significant advantage over on-demand regimens in a diabetic population.[265]

Several clinical trials have demonstrated the effectiveness of PDE5is in improving ED in men with DM (**Tabl.1**). A recent meta-analysis of 12 clinical trials including 3124 men with DM and 6 PDE5is showed that PDE5is significantly improved erectile function compared with placebo, as measured using the IIEF, SEP and GAQ questionnaires, with a good safety profile and tolerability.[266] Another systematic review and meta-analysis found that all PDE5is showed similar effectiveness, with slightly superior response rates for sildenafil over tadalafil and vardenafil,[267] However, considering variations in the efficacy reported across the studies, superiority of one medication over the other cannot be determined. Conversely, in 2018, Liao et al. performed SUCRA and NMA analyses of data from 15 RCTs involving patients with DM, demonstrating a possible advantage of vardenafil and mirodenafil over other PDE5is in terms of efficacy and adverse effects, with an overall greater efficacy–safety profile.[265]

Sildenafil

Sildenafil was the first oral drug approved for ED treatment in 1998.[268] In addition to PDE5 inhibition, sildenafil also weakly inhibits PDE6, an enzyme present at high concentrations at the retinal rod and cone photoreceptors, potentially leading to mild impairment in colour discrimination during peak plasma levels approximately 1 h after drug ingestion.[269]

A recent meta-analysis of eight RCTs that compared the effectiveness of sildenafil at dosages varying from 25 to 100 mg to that of placebo in patients with DM who had ED reported an overall response rate of 57.7%, with a significant improvement in IIEF scores (particularly for questions 3 and 4) and a relative risk of 3.99 for answering ‘yes’ to the global efficiency question (95% CI, 2.58–6.18) in sildenafil users.[257] The most common adverse events included headaches, dyspepsia and flushing, with their intensities ranging from mild to moderate, resulting in a 2.4% discontinuation rate in the sildenafil arm.

In addition to on-demand regimens, daily sildenafil administration has also been studied. In a double-blind placebo-controlled RCT, 24 men with DM were assigned to receive daily sildenafil 50 mg or placebo. After 10 weeks, their IIEF scores and endothelial function, monitored via brachial artery flow-mediated dilatation, improved.[270] Similarly, Price et al. reported an improvement in erectile activity in 21 men receiving sildenafil 50 mg daily.[271]

Vardenafil

Vardenafil, which is available in two formulations (a film-coated tablet and an orodispersible tablet), is generally well tolerated but should be avoided in patients with prolonged QT interval or in men using antiarrhythmic drugs such as procainamide, quinidine, sotalol, or amiodarone.[272] Similar to sildenafil, vardenafil weakly inhibits PDE6 and may have similar side effects on retina photoreceptors.[273]

Several studies have analysed the effectiveness of vardenafil in patients with DM. Accordingly, a 12-week prospective, multi-centre, double-blind, placebo-controlled, fixed-dose, parallel-group trial with 452 patients with DM reported an improvement in erections in 57% of men taking vardenafil 10 mg and 72% of men taking vardenafil 20 mg compared with 13% of those receiving placebo.[274] Moreover, an improvement of 5.9 and 7.8 points in the EF domain of the IIEF for vardenafil 10 and 20 mg had been observed, respectively, with the placebo group showing an improvement of 1.4 points. There was no correlation between HbA1c levels and vardenafil effectiveness. Adverse events, mostly headache, flushing and rhinitis, were reported as mild to moderate by 13% of the patients.

Similar results were reported by Ishii et al.[275] in an RCT involving 778 patients with DM, with a mean IIEF improvement of 7 points in the 10 and 20 mg vardenafil groups and a response rate of 63% and 57% for men allocated to the 20 and 10 mg group, respectively, with greater response rates in patients with severe ED.

Chronic vardenafil therapy also appeared to be effective and may improve hypogonadism in hypogonadal men with DM. In a 2016 placebo-controlled RCT with 54 patients with DM, vardenafil (10 BID) resulted in higher IIEF-15 and flow-mediated dilatation scores. Interestingly, total testosterone levels, measured using liquid chromatography, increased to normal levels in hypogonadal patients in the vardenafil arm.[276]

Tadalafil

Tadalafil has the longest half-life among PDE5is (17.5 h), with a duration of action of 24–36 h.[277] Owing to the drug's delayed metabolism, its pharmacokinetic properties are not affected by food ingestion and gastric emptying.[278] Tadalafil is also able to inhibit PDE11, with this interaction having been thought to be responsible for some of its adverse effects, such as myalgia and back pain.[279]

Tadalafil is suitable and has been approved for both low-dose daily use (2.5–5 mg) and on-demand use for ED treatment. Both treatments were found to be successful in the management of ED among patients with DM. In

a meta-analysis of 12 RCTs including 637 patients with DM, the use of tadalafil 20 mg resulted in a 53% response rate and a mean improvement in their IIEF score of 7.4 points, with the placebo group showing a 0.9 point improvement, independent of glycaemic control.[256] Similarly, a 12-week placebo-controlled RCT involving 298 patients with DM found that daily use of tadalafil 2.5 or 5 mg promoted significant improvements in both IIEF and SEP2 and SEP3 scores, with response rates of 41% and 46%, respectively.[280] The most frequent adverse events included headaches, myalgia and back pain, which were classified as mild-to-moderate in most cases. Interestingly, in addition to its effectiveness in ED treatment, daily use of tadalafil seemed to be effective in improving endothelial dysfunction, one of the most important pathogenetic factors in diabetic ED.[281]

A recent single-centre retrospective clinical study comparing the effects of tadalafil 5 mg daily and 20 mg OD in patients with DM revealed that both regimens promoted similar IIEF improvements in patients aged <65 years, whereas only the daily regimen facilitated significant improvements in patients aged >65 years. Both treatments also improved LUTS, with greater benefits observed in the 5-mg group.[282]

Avanafil

Avanafil, which was approved in 2012 for the management of ED, is highly selective for PDE5 versus other PDE isoenzymes such as PDE1, PDE5 and PDE11. This may result in better safety profiles in terms of lower incidences of adverse events such as visual disturbances, myalgia and back pain.[283] Although avanafil is generally well tolerated, it should not be administered to patients with severe liver damage.[284]

Avanafil's effectiveness in patients with DM was evaluated in an RCT with 390 men with DM experiencing ED over a period of 12 weeks. Avanafil 100 or 200 mg resulted in significant improvements in the IIEF-EF domain, SEP2 and SEP 3 compared with placebo. The adverse events were similar to those observed with other PDE5is.[285]

Udenafil

Udenafil is a novel PDE5i that is approved in only a few countries, such as Korea, Russia and the Philippines. Based on data from clinical trials, udenafil has a half-life of approximately 11–13 h and a duration of action

of 24 h.[277] Considering its pharmacokinetic properties, it could be used both once daily and on-demand. Studies in patients with diabetes have confirmed the efficacy of both regimens.[286,287]

A 12-week, placebo-controlled, double-blind, parallel-group study involving 147 men with DM experiencing ED found that the use of udenafil 100 mg and 200 mg resulted in significant improvements in the IIEF-EFD score, SEP diary and GAQ, with no significant differences between the 100- and 200-mg groups.[286] The most frequent adverse events included flushing, headaches, nausea and conjunctival hyperaemia, which were reportedly mild in most cases.

Similar results were obtained in a 12-week study that compared udenafil 50 mg once daily and udenafil 200 mg on-demand in men with DM previously treated with idenafil 200 mg.[287] At the end of the 8-week intervention period, both groups had similar improvements in IIEF-EFD (10.78 points for 200 mg and 9.97 points for 50 mg daily), SEP Q2 and Q3 and GAQ. These improvements were not maintained during the 4-week drug-free period. Both regimens were well tolerated, with flushing and headaches recorded as the most frequent adverse events.

Mirodenafil

Mirodenafil is a second generation PDE5i with high selectivity for PDE5 over other PDE isoforms. Despite its high PDE5 selectivity, mirodenafil has a slightly greater affinity for PDE6 than sildenafil. However, no visual adverse effects have been reported in men taking mirodenafil to date.[288]

Mirodenafil is an effective and well-tolerated therapy in a broad range of patients with ED.[289] In the treatment of diabetic ED, 100 mg mirodenafil has been shown to have a positive impact on IIEF-EF scores (9.3 ± 6.8 vs. 1.4 ± 6.1 in the placebo group), SEP2, SEP3 and GAQ, with a response rate of 61.8%.[290] The reported adverse events mostly included headaches and flushing, which were mild in intensity without serious adverse events.

PDE5is and TRT

Despite PDE5is being an effective treatment for diabetic ED, up to 50% of subjects failed to respond to this drug class.[259] Given the high prevalence of hypogonadism in patients with DM,[291] reduced testosterone levels have been speculated to contribute to the unresponsiveness of PDE5is in this subpopulation.

A recent meta-analysis showed that TRT alone was able to significantly improve erectile function and other sexual parameters in hypogonadal men, with higher benefits for patients with more severe hypogonadism (total testosterone < 8nmol/L) and lesser benefits for those with comorbidities such as DM and obesity.[292] These findings may be due to the presence of concomitant micro- and macrovascular complications and endothelial dysfunction, in addition to the more severe testosterone deficiency noted in this population. Testosterone therapy, however, has been shown to ameliorate sexual health as well as improve insulin resistance and lipid profile in hypogonadal men with DM.[116]

Nonetheless, whether testosterone replacement is able to increase the effectiveness of PDE5is remains inconclusive. A meta-analysis of 12 RCTs evaluating the effects of testosterone therapy together with PDE5is showed a positive effect in uncontrolled studies but not in placebo-controlled studies.[293] However, three of the five placebo-controlled RCTs enrolled mixed eugonadal/hypogonadal patients, whereas in another trial, testosterone therapy was started after a sildenafil alone run-in period when subjects had already achieved eugonadism.[294] In another study, testosterone therapy had no effect on sexual function in subjects without testosterone deficiency at baseline.[295]

Multiple studies have shown that restoring sexual activity in patients with ED using PDE5is can increase testosterone levels[296,297] and restore eugonadism.[294] Therefore, PDE5i-only therapy may be useful for men with mild hypogonadism related to diminished sexual activity caused by anxiety or other psychological disorders. If hypogonadism persists, testosterone replacement should be started. The TADTEST study showed that adding testosterone to daily tadalafil therapy in subjects unresponsive to PDE5is was beneficial only in hypogonadal men with baseline testosterone levels of ≤3 ng/mL, suggesting the need for testosterone therapy in subjects with a higher degree of testosterone deficiency.[298]

Similarly, the administration of parenteral testosterone undecanoate for 102 weeks to 29 men with DM who were unsuccessfully treated for ED with PDE5is with subnormal plasma testosterone levels (total testosterone < 3.5 ng/mL) resulted in higher IIEF scores as well as improvement in MetS parameters.[299]

Clinical studies have shown that PDE5i use alone can increase testosterone levels by approximately 3–6 nmol/L in healthy subjects and 2–4 nmol/L in patients with DM.[300] This is unlikely to lead to adequate levels in men with severe hypogonadism, especially when secondary to a clearly identified cause. As such,

testosterone replacement is preferred in these subjects given its ability to restore sexual function alone, with the option of adding PDE5is when results are unsatisfactory.

Finally, androgen therapy can improve several diabetes-related comorbidities other than ED; therefore, these aspects should be considered to initiate adequate treatment.

PDE5is and the cardiovascular system

Over the past decade, considerable interest has emerged regarding the benefit of PDE5is in CVD associated with T2DM. T2DM and CVD show similar alterations, such as increased levels of pro-inflammatory factors, endothelial dysfunction and decreased nitric oxide-mediated vasodilation.[301] Therefore, it is unsurprising that PDE5i therapy can exert cardioprotective effects in patients with DM.

Data from retrospective and observational studies have shown that PDE5is can reduce age-related mortality in men with T2DM,[302] as well as all-cause mortality and MI incidence and mortality.[303]

Although not fully understood, the mechanisms by which PDE5is are able to ameliorate cardiovascular derangements in T2DM seem to involve improvement of endothelial dysfunction, systemic inflammation and nitric oxide bioavailability.[301]

Studies have shown that treatment with sildenafil, vardenafil and tadalafil improved FMD, a measure of nitric oxide-mediated endothelial function,[304] vascular inflammation markers and endothelin-1 levels.[305,306] Interestingly, the cardiovascular and endothelial benefits of PDE5i seem to be independent of glycaemic control[307], as evaluated by HbA1c levels. PDE5i treatment has also been shown to reduce the levels of pro-inflammatory factors such as Il-6, Il-8, TNF-α, CXCL-10 and IL-1β[306,308,309] in both humans and animal models.

The effects of PDE5is on diabetic cardiomyopathy and related complications is another promising field that has recently been explored. Results from animal models showed that tadalafil could reverse alterations in cytoskeletal/contractile proteins in the heart, attenuate mitochondrial dysfunction,[310,311] and reduce infarct size induced by ischaemia reperfusion.[308] Vardenafil was also found to be effective in reducing myocardial hypertrophy and fibrotic remodelling,[312] decreasing apoptosis and nitro-oxidative stress via the cGMP–PKG pathway, whereas sildenafil-treated mice showed improved cardiomyocyte contractility[313] due to enhanced cGMP–PKG and phosphodiesterase 3-dependent cAMP signalling.

PDE5i-mediated augmentation of NOS3 activity in the heart and mitochondrial ATP-sensitive potassium channel opening have been shown to reduce ischaemia/reperfusion injury, infarct size and the incidence of cardiomyocyte death.[314,315] Similarly, PDE5is-mediated augmentation of the cGMP–PKG pathway appeared to ameliorate the clinical condition of patients with heart failure with reduced ejection fraction through improvements in pulmonary circulation, cardiac remodelling and diastolic function[316] but had few effects in patients with reserved ejection fraction.[317] Other trials, however, have demonstrated increased cardiac performance,[318,319] such as left ventricle diastolic function, cardiac geometry and clinical status, in patients with T2DM.

Despite being used for ED, PDE5is clearly have favourable effects on the cardiovascular system, primarily due to the restoration of the NO–cGMP–PKG signalling pathway and amelioration of the pro-inflammatory state that characterises T2DM and the consequent endothelial dysfunction and increased cardiovascular risk. Although results from preclinical and human studies have been promising, additional studies are needed to determine the role of PDE5is in cardiovascular protection in T2DM.

Other treatments for ED

For patients unresponsive to medical and lifestyle treatments, several second- and third-line therapies are available, the most popular of which is alprostadil (prostaglandinE1 [PGE1]). It can be used in the form of a urethral suppository, which was first marketed as medicated urethral system for erection, via intracavernosal injections, directly into the corpora cavernosa via a small needle, or as a topical cream. PGE1 increases cAMP levels via adenylate cyclase stimulation, leading to smooth cell relaxation, vasodilation and penile erection.

Intracavernosal alprostadil has been one of the oldest and most effective treatments for ED in individuals with DM. Accordingly, studies conducted in patients with both T1DM and T2DM have showed satisfactory sexual activity and intercourse after 76.5%–99% of alprostadil injections.[320,321] The most reported adverse event was penile pain, in 24%–61% of patients, although this was tolerable in most of the patients. Priapism and fibrosis have also been found to occur after alprostadil injections, albeit rarely.[322] Interestingly, a combination of alprostadil and α-lipoic acid, administered as an intracavernosal injection, was more effective (95.0% vs. 80.5%, $p < 0.05$) than tadalafil (5 mg) and was able to improve vascular endothelial function and erection hardness with a good safety profile.[323] Despite the need for injections and possible injection-related issues

(pain/difficulty), alprostadil injections have been found to be a safe and effective alternative in the long term, although a mixture of different vasoactive drugs, such as papaverine and phentolamine, instead of PGE1 alone has often been used.[324] Patients with diabetes, especially those using insulin therapy, have higher compliance with self-injections compared to those without diabetes.[325] After years of treatment, however, they usually reduce injection frequency and may stop treatment, necessitating frequent follow-up visits with dosage adjustments to prevent dissatisfaction and drop-out from treatment, which occurs in up to 68% of patients in the first 3 months.[326]

Intraurethral alprostadil consists of a polypropylene applicator with a pellet of alprostadil at its tip. Although its overall efficacy rate is approximately 60%,[327] it causes dose-dependent penile pain and burning in 10% of treated patients. Despite its lower efficacy compared to intracavernosal PGE1 injections, the lack of injection-related issues and its easy administration makes it appealing for patients that dislike injectable therapies. In fact, one trial showed that intraurethral alprostadil was effective in up to 65% of patients with DM, with variable efficacy based on the severity of ED.[328]

Alprostadil cream can be another promising treatment for ED. Phase 2 and 3 trials have found that alprostadil cream administered into the external urethral meatus promoted adequate erection in 74%–83% of patients,[329,330] with similarly good results in populations with diabetes and those unresponsive to PDE5is.

Among the other treatments, vacuum erection devices represent a non-invasive alternative, which has been initially effective in approximately 90% of patients. It is a cylindrical mechanical device which is placed over the penis and pumped; consequently, it creates a negative pressure vacuum to draw blood into the penis.[331] However, these devices are often heavy and uncomfortable to use, with 64% patient discontinuation rates at 2 years.[332] Trials among individuals with diabetes showed that vacuum devices are effective in up to 75% of users,[333] with improvements in psychological status, peak systolic velocity and diameter of cavernosal artery evaluated using Doppler colour flow imaging[334] after 6 months of treatment. Vacuum devices in combination with sildenafil in men with diabetes promoted better successful penetrations (73.3% vs. 46.6%) and successful intercourses (70% vs 46.6%) at 3 months compared to sildenafil alone,[335] with higher Mean International Index of Erectile Function scores. The most reported adverse events included penile pain, numbness and bruising.

Among the surgical approaches for ED, penile prosthesis is the most attractive and effective option for patients unresponsive to medical and second line treatments. This approach represents a permanent solution for the problem.

Penile implants include malleable and inflatable devices. The malleable implant consists of two semi-rigid rods that are placed in the corpora cavernosa, and it is bent upwards before intercourse. On the other hand, two-piece inflatable penile prostheses involve two cylinders with a scrotal pump, which allows fluid to be transferred to the cylinder chambers when an erection is desired.[336]

Despite being a substantially effective treatment for ED, with satisfaction rates greater than 95%,[337,338] men with diabetes seem to be more prone to developing prosthesis infections.[339] The risk, however, has reduced over the decades with device improvement and surgical expertise,[340] with evidence identifying short-term glucose control (BG >200 mg/dL), but not HbA1c levels, as the strongest risk factor for prosthesis infection.[341] Finally, penile revascularization surgery techniques were developed in order to anastomose the inferior epigastric artery to either the dorsal artery or deep dorsal vein, to improve penile vascular inflow while reducing venous outflow; however, no standardized method is available. [258]

Conclusions

This review underscores and confirms the importance of appropriately managing patients with DM experiencing ED, highlighting the role of comorbidities, complications and the role of anti-diabetic drugs. In this regard, both metformin and new anti-diabetic medications seem to play a protective role in ED pathogenesis. Finally, evidence shows that PDE5is could be considered safe and beneficial for CVD associated with T2DM.

Figure and Table legend:

Figure 1. Diabetes and erectile dysfunction: a complicated connection.

The major complications and comorbidities related to diabetes (DM) that contribute to erectile dysfunction (ED) are shown in the figure. The graphic representation shows the major diabetes (DM) complications and comorbidities that contribute to erectile dysfunction (ED). DM complications are associated with endothelial impairment and can be distinguished in macrovascular (cardiovascular events) and microvascular

(nephropathy and neuropathy). The major diabetes comorbidities which lead to ED are hypogonadism, metabolic syndrome (obesity, hypertension, dyslipidemia), obstructive sleep apnea and depression.

The picture shows how the single pathologies are strictly interconnected: thus, increasing the incidence of ED with the number and severity of comorbidities as indicated by arrows, each individual disease can worsen DM complications and increase the incidence and number of comorbidities, thus increasing the incidence and severity of ED.

Abbreviations: MetS: Metabolic Syndrome; OSAS: Obstructive Sleep Apnea Syndrome; UTI: Urinary Tract Infection; CV: Cardio Vascular.

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PDE5i							
Author	**Study design**	**N° of patients**	**Disease**	**Mean or range age**	**Intervention**	**Methodologies and scale**	**Results**
Price et al. 1998	Prospective, DB, PC, three-way crossover study	21	T2DM	42-65	In part I single dose sildenafil 25-50 mg or placebo In part II once-daily dosing sildenafil 25-50 mg or placebo For 10 days	penile plethysmography daily diary records of erectile activity and a global efficacy question	Improvement in penile rigidity and erectile activity
Rendell et al. 1999	Prospective, RCT, DB, PC, flexible-dose	268	T1 and T2DM	57	Sildenafil 25-50-100 mg or placebo	IIEF	56% of sildenafil improved their erections vs. placebo
Boulton et al. 2001	Prospective, PC, DB, and flexible-dose escalation study	219	T2DM	59	Sildenafil 50 mg (25-50-100 escalation/adjusting)	IIEF	Improved in EF domain (mean value 10.0)
Safarinejad et al. 2004	Prospective, RCT, PC, DB	282	T2DM	46.4	Sildenafil 100 mg or placebo	IIEF	59% of patients improved their IIEF
Behrend et al. 2005	Prospective, self- reported, flexible-dose	33	T1 and T2DM	58.1	Sildenafil 25 to 100 mg	IIEF	Improved IIEF score (mean value 16,9)
Blonde et al. 2006	Retrospective analysis of pooled data from RCT PB	974	T2DM	57	Flexible-dose sildenafil (25, 50, or 100 mg) or placebo	IIEF	Improvement in erections (62% vs. 18%) and in percentage of successful sexual intercourse attempts (52.6 +/- 5.0 vs. 22.4 +/- 5.1)
Deyoung et al. 2011	Prospective, RCT, DB, PC	24	T2DM	59.8 (plb) 59.4 (50 mg)	Daily sildenafil 50 mg Or placebo	IIEF-5	Improved IIEF-5 and FMD (2-fold increase in the brachial artery diameter)
Utku Kirilmaz et al. 2015	Prospective, open RCT	83	T2DM	54.9	Sildenafil 100 mg in addition to lifestyle modifications and glycemic control	IIEF	Improved IIEF: 5.0 points for sildenafil vs 2.5 control
Goldstein et al. 2003	Prospective, DB, PC, fixed-dose parallel-group	452	T1 and T2DM	57	Vardenafil 10 or 20 mg or placebo	IIEF	Improved IIEF (5.9/7.8 for 10/20 mg respectively)
Ziegler et al. 2006	Prospective, RCT, PC, DB	302	T1DM	50.3	Vardenafil 5-20mg flexible dose or placebo	IIEF	Improved EF (mean value 7.79)
Ishii N et al. 2006	Prospective, RCT, DB, PC, multi-centre, parallel	778	T2DM	26-64	Vardenafil 10 or 20 mg or placebo	IIEF	Improved EF domain score (mean value 7 for both)
Daniele santi et al. 2016	Prospective, DB PC RCT	54	T2DM	55.8	Vardenafil 10 mg BID or placebo	IIEF, FMD, testosterone level	Higher IIEF and FMD scores in Vardenafil group. Total testosterone increased in hypogonadal diabetic subjects in vardenafil group

Sáenz de Tejada et al. 2002	Prospective, RCT, DB, PC	191	T2DM	55.7	Tadalafil10-20mg or placebo	IIEF	Improvement of erections in 56% and 64%, respectively *vs.* 25% of placebo
Fonseca et al. 2004	Prospective, RCT, DB, PC parallel group	637	T2DM	57	Tadalafil 10 mg, 20 mg, or placebo	IIEF	Mean improvement of 7.4 in IIEF
Buvat et al. 2006	Prospective, randomized, crossover, open-label	762	T1 and T2DM	57	Chronic vs. On-demand of tadalafil 20 mg	IIEF, SEP	Mean improvement of 9 points in IIEF and 44 of SEP
Hatzichristou et al. 2008	Prospective, RCT, DB, PC	298	T2DM	58 (plb) 57 (2.5 mg) 56 (5 mg)	Tadalafil 2.5 mg, tadalafil 5 mg or placebo	IIEF, SEP GAQ	Improvements in IIEF and in mean success rates for vaginal penetration, completion of intercourse, and overall treatment satisfaction.
Mustafa Suat Bolat et al. 2018	Single center retrospective study	63	T2DM	60.5 (5 mg) 60.9 (20 mg)	Tadalafil 5 mg daily or Tadalafil 20 mg on demand	IIEF, IPSS, MSHQ, EHS	Improvement in IIEF: mean 3/2,3 (<65y) respectively and 2,8 (>65y only 5mg group); improvement in IPSS, MSHQ and EHS
Goldstein et al. 2012	Prospective, RCT, DB, PC	390	T2DM	58	Avanafil 100/200mg or placebo	IIEF	Improvement of IIEF 4.5/5.4 points respectively
Moon et al. 2011	Prospective, RCT, DB double-dummy, parallel-group design multicenter study, fixed-dose trial	174	T2DM	55	Udenafi 100 or 200 mg or placebo	IIEF	Improvements in the IIEF-EFD score
Soon Hyun Park et al. 2015	Prospective, multi-center, randomized, open-label, parallel-group	161	T2DM	54.4 (50 mg) 53.9 (200 mg)	Udenafil 50 mg once-daily or Udenafil 200 mg on demand	IIEF, GAQ, SEP	Similar improvements in IIEF, SEP and GAQ
Hyun Jun Park et al. 2010	Prospective, multicenter, DB, PC, parallel-group, fixed-dose RCT	112	T2DM	55.5 (plb) 57.3 (100 mg)	Mirodenafil 100 mg or placebo	IIEF, GAQ, SEP	Improvement in IIEF-EF domain scores (9.3 +/- 6.8 vs. 1.4+/- 6.1); SEP2 SEP3 and GAQ improved

Table 1. Clinical trials considering PDE5is in men with diabetes.

PDE5is: phosphodiesterase type 5 inhibitor; ED: erectile dysfunction; T1DM and T2DM: Type 1 and Type 2 Diabetes Mellitus; RCT: randomized controlled trial; PC: placebo controlled; DB: double blind; TID: three times a day; BP: blood pressure; NK: not know; ED: erectile dysfunction; IL-6: interleukin 6; CRP: c reactive protein, IIEF: International Index of Erectile Function; ET endothelial; SEP: Sexual Encounter Profile; GAQ: Global Assessment Questions.