# The management of erectile dysfunction in men with diabetes mellitus unresponsive to Phosphodiesterase type 5 inhibitors


## AUTHORS

- Axel Alberto Cayetano-Alcaraz. draxelcayetano@andrologia.com.mx. Imperial College Healthcare NHS Trust, Charing Cross Hospital. Urology department. London, United Kingdom.
- Tharu Tharakan. Tharu.tharakan05@imperial.ac.uk. Imperial College Healthcare NHS Trust, Charing Cross Hospital. Urology department. London, United Kingdom.
- Runzhi Chen. run-zhi.chen16@imperial.ac.uk. Faculty of Medicine, Imperial College London, Imperial College Rd, London, UK.
- Nikolaos Sofikitis. v.sofikitis@hotmail.com. University of Ioannina School of Medicine, Urology Department, Greece.
- Suks Minhas. sminhas@btinternet.com. Imperial College Healthcare NHS Trust, Charing Cross Hospital. Urology department. London, United Kingdom.



## ABSTRACT

**Introduction**.

Erectile dysfunction (ED) is associated with diabetes mellitus with an estimated prevalence of 52.5% in the diabetic population. The first-line therapy for ED are phosphodiesterase type 5 inhibitors (PDE5i), but data suggests that diabetic men may be less responsive than non-diabetic men. Thus, other treatments, including intracavernosal injections, intraurethral prostaglandin, vacuum erection devices, and penile prosthetic surgery, should be considered in management of diabetic men with ED refractory to PDE5i. Furthermore, combination therapy of PDE5i and other oral treatments such as arginine or L-carnitine may have synergistic effects resulting in better outcomes. In addition, there are novel therapies such as low-intensity shockwave therapy and stem cell therapy which may also be effective targeted treatment modalities. Furthermore, studies suggest that ED can be improved by targeting concurrent comorbidities or metabolic diseases such as depression, hypertension,


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hypogonadism, and dyslipidaemia. We present an evidence-based narrative review focussing on the management of ED in diabetic men who have not responded to PDE5i.

**Conclusions**

Both clinicians and patients should be aware of the different management options in Diabetic patients who have responded to PDE5i.

## KEYWORDS

Erectile dysfunction

Diabetes Mellitus

Diabetes Complications/*complications

Penile Prosthesis

Phosphodiesterase 5 Inhibitors

Non-responders to PDE5I

Low-intensity extracorporeal shockwave therapy

Drug Therapy, Combination

Stem cell therapy

Intracavernosal injection therapy

Antioxidants

Hypogonadism

vacuum pump

## INTRODUCTION

Erectile dysfunction (ED) has a prevalence of 52.5% in diabetic male patients, as described in a metanalysis of 145 studies, including 88 577 men with type 1 and Type 2 diabetes.[1] In the same metanalysis, a significant association was found between diabetes mellitus (type 1 and type 2 diabetes, n = 863) and the odds of having ED (OR 3.6, 95% CI, 2.5- 5.6, P < 0.0001) compared with healthy controls (n = 5385) [1]. Furthermore, in the Massachusetts Male Aging Study, the age-adjusted probability of ED was 3 times greater in diabetic patients than those without diabetes[2].

The first-line therapy for ED in diabetes mellitus (DM) is PDE5 inhibitors (PDE5i). However, DM patients appear to be less responsive to these pharmacological agents compared to men without DM. This is supported in an in vitro study by Angulo et al. where relaxation of human corpus cavernosum strips from diabetic and non-diabetic patients with ED were compared and lower basal and stimulated levels of cGMP (cyclic guanosine-monophosphate) were found in strips of corpus cavernosum from men with DM[3]. Therefore, a patient-centred and tailored approach with an understanding of the pathophysiological mechanisms and the pharmacology of each therapy will optimise outcomes and patient satisfaction.

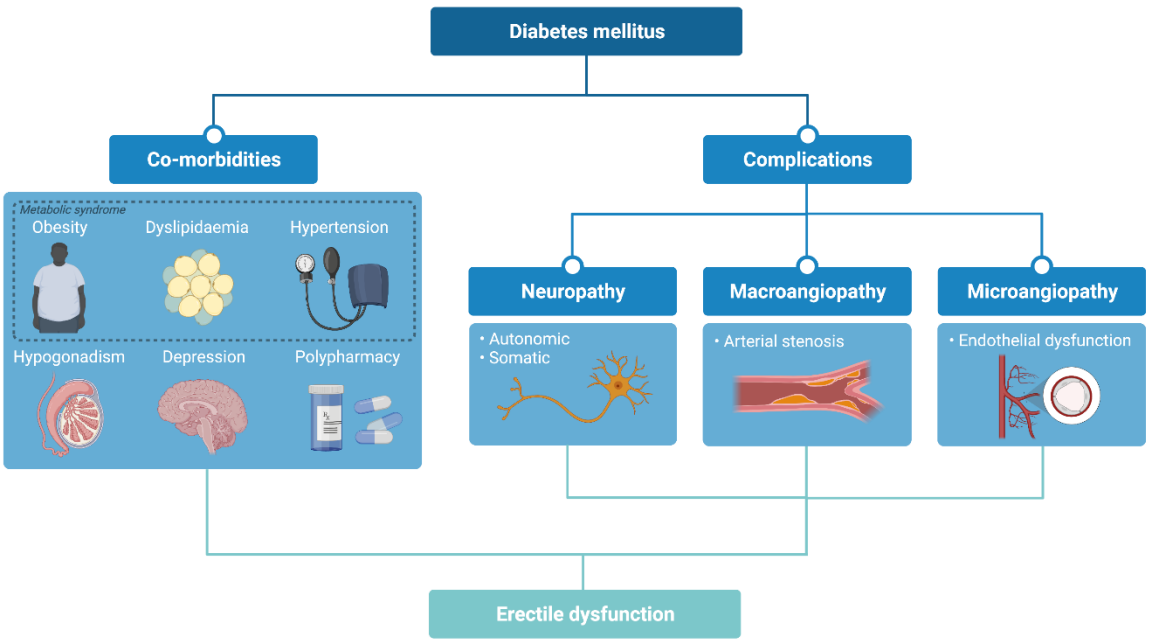
This narrative review is focused on the pathophysiology of ED in diabetic patients and the main treatment options in men who have not responded to PDE5i.

## PATHOPHYSIOLOGY

In order to understand the optimal management of ED in diabetic men, one must appreciate the pathophysiological mechanisms of ED in men with DM and also the common comorbidities associated with ED and DM.

ED in DM patients can be caused by vascular, neuropathic, psychological, and endocrine factors. Moreover, ED and DM share common risk factors including metabolic syndrome, hypertension, cardiovascular disease, obesity, and depression (Figure 1)[4-7].

Figure 1. Physiopathology of erectile dysfunction in diabetic patients. Modified from Defeudis et al. and Kamenov et al.[8,9]




### ATHEROSCLEROSIS

DM causes accelerated formation of atherosclerotic plaques[10,11] through endothelial dysfunction, inflammation, oxidative stress and immune response[11]. Hence DM is associated with both peripheral vascular and cardiovascular disease. A number of studies have demonstrated impaired endothelial dysfunction in the corpora cavernosum of diabetic men and animals. Given that the arterial vasculature of the penis is much smaller than other vessels (such as coronary arteries)[12], ED often precedes cardiovascular disease and is recognised as a warning sign of occult cardiovascular disease[13]. Therefore, men presenting with ED should be screened for atherosclerotic risk factors (DM, HTN, High cholesterol)[14].

**NEUROPATHY**

DM leads to decreased medicated smooth muscle relaxation of the corpus cavernosum, as a result of impaired NO (Nitric oxide) production[15,16]. This has clinical implications because severe neuropathy can affect PDE5i efficacy, which requires a minimum level of NO to function effectively[17] and is likely to be one mechanism for a reduced response to PDE5i in diabetic compared to non-diabetic men[3].

In addition to this, recent cohort studies showed the predictive capability of diabetic neuropathy in the development of ED. For example, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Study (DCCT/EDIC) observed that patients with Type 1 DM with cardiovascular autonomic neuropathy had an OR of 2.65(95% CI 1.47-4.79) for developing erectile dysfunction and lower urinary tract symptoms[18].

**MICROANGIOPATHY**

DM can affect both corpus cavernosum relaxation and oxidative stress regulation. DM results in lower baseline Nitric oxide (NO) levels in the corpus cavernosum, irrespective of cGMP stimulation, and combined with impaired endothelium-dependent relaxation of the corpus cavernousum results in impaired smooth muscle relation [3].

The penile expression of VEGF (Vascular Endothelial Growth Factor) is diminished in diabetic models. For example, in rat models of type 2 diabetes, using immunohistochemistry and quantitative PCR, the protein and mRNA expression of penile VEGF was reduced compared to control animals; mRNA levels of VEGF were 58% less than levels in control animals[19]. Given that VEFG regulates endothelial cell proliferation, angiogenesis, and anti-apoptosis, this may be another mechanism for ED in DM[19].

Data shows that chronic hyperglycemia can increase oxidative stress due to inflammation, elevated production of reactive oxygen species (ROS), hyperhomocysteinemia, and reduced cellular antioxidants.[20-23] Morano et al. demonstrated higher levels of oxidative activity in circulating monocytes of patients with DM and ED than in diabetic patients without ED (mean± standard error of mean oxidation index, 9.3±1.6 vs 4.8±0.5, $p < 0.03$, respectively)[21].

## COMMON DIABETIC COMORBIDITIES ASSOCIATED WITH ERECTILE DYSFUNCTION

### METABOLIC SYNDROME AND OBESITY

DM is associated with both obesity and metabolic syndrome[24,25]. Furthermore, there is a positive correlation between the degree of abdominal obesity and the prevalence of metabolic syndrome and erectile dysfunction[26,27]. The proportion for patients (n = 216) with some degree of ED measured by the International Index of Erectile Function 5 (IIEF5) score increased proportionally with the degree of abdominal obesity (61%, 68%, 83% and 87% for grade 1, grade 2, grade 3 and grade 4 abdominal obesity, respectively). A similar correlation was also found in the prevalence of metabolic syndrome in 35%, 51%, 84.5% and 84%, of patients respectively[26].

Waist circumference (WC) is positively correlated to the severity of ED (r = 0.16, p = 0.001, n = 417), even after controlling for associated comorbidities (smoking, hypogonadism, depression and prostate symptoms); for 1cm increase in WC, there is a 3% increase risk of having ED[28]. Also, the European Male Ageing Study found that men with a high BMI (>30kgm2) or high WC (>102 cm) had almost twice the risk of having ED in multivariable logistic regression models (OR for high BMI 1.8, 95% CI: 1.4-2.3; OR for high WC 1.73, 95% CI: 1.50–1.98)[27].

Not surprisingly, there is a direct association between ED and metabolic syndrome. In 2013, García-Cruz et al. observed in a multicentre and cross-sectional study that moderate and severe ED were significantly associated with higher odds of having metabolic syndrome in a multivariate analysis (OR 3.2, 95% CI 1.3-7.8 and OR 4.7, 95% CI 1.8-11.9, respectively)[29].

Epidemiologic studies showed an association between low serum 25(OH)$D_3$ concentration and an increased risk for metabolic syndrome and type 2 diabetes[30,31]. There might be a multidirectional relationship between vitamin D deficiency and ED. In 2020, A meta-analysis of observational studies exploring the link between ED and vitamin D deficiency showed that 183 pooled patients with Vitamin D deficiency had lower IIEF5 scores than 161 controls (standardised mean difference [SMD] -0.59, 95% CI -1.06 to -0.11, $I^2$=72%)[32]. In the same sense, another meta-analysis showed lower total testosterone concentrations in men with Vitamin D deficiency (<20 ng/mL) in 9892 men with vitamin D deficiency (pooled SMD -0.23, 95%CI -0.45 to -0.01, p= 0.04, $I^2$=98%)[33]. There is a lack of evidence on whether the role of Vitamin D supplementation helps treat ED in the diabetic population.

### DYSLIPIDAEMIA

Dyslipidaemia is associated with type 2 DM, specifically, increased triglyceride levels, decreased high-density lipoprotein (HDL), and high small dense LDL.[34] Regarding type 1 diabetes, in poorly controlled patients, there are alterations similar to type 2 DM, including high non-HDL cholesterol[35]. In addition, dyslipidaemia is a contributing factor for atherosclerotic cardiovascular disease, as stated by the 2018 Guideline on the Management of Blood Cholesterol (American College of Cardiology / American Heart Association Task Force)[36], and therefore is a risk factor for ED.

### HYPOGONADISM

Low testosterone levels are prevalent in patients with metabolic syndrome and diabetes[37]. The estimated prevalence of hypogonadism in DM ranges from 24 to 33%[38,39]. Accordingly, current

endocrine guidelines such as the American Diabetes Association (2020) recommend routine measurement of testosterone in men with DM[37].

A meta-analysis of 14 RCTs (n = 2298) reported that testosterone replacement therapy improved IIEF- erectile function scores compared with placebo in patients with late-onset hypogonadism (mean difference= 2.31, CI 95% 1.41-3.22, p <0.0001)[40]. Furthermore, with lower baseline serum testosterone levels, greater benefits were observed in the IIEF-EFD (Erectile Function Domain) with TRT. However, the benefit of hormone therapy on the IIEF score effect was reduced in men with diabetes and high body mass index[40].

Hypogonadal patients could improve their response to PDE5i if appropriate hormone replacement therapy is started[41]. As demonstrated in a metanalysis of 7 non-placebo-controlled RCT, the mean difference in IIEF scores favoured testosterone supplementation plus PDE5i vs PDE5i alone (0.69, 95% CI 0.23-1.15, p <0.05)[42].

Long-term testosterone supplementation for hypogonadal patients with type 2 diabetes improves different sexual domains. The BLAST study, a double-blinded and placebo-controlled study, showed improvements in this population after receiving treatment with testosterone undecanoate. After 30 weeks of treatment, the IIEF-15 score increased by 4.31 points from baseline; mainly, there were improvements in intercourse satisfaction(p=0.005), sexual desire (p=0.001), overall satisfaction (p=0.05) and orgasm (p=0.04) compared to placebo group[43]. Also, this study showed that baseline depression dampens the improvement in sexual function even after hormone replacement therapy[43].

The BLAST study found better outcomes in severe hypogonadism (defined as TT <8.0 nmol/l or free testosterone 0.18 nmol/l) for erectile function (IIEF 9.15±1.5 to 13.04±2.04, p=0.029), intercourse satisfaction (IIEF 3.19±0.75 to 5.26±0.98, p = 0.020) and sexual desire (IIF 4.04±0.35 to 5.74±0.47, p < 0.001). In contrast, the placebo group showed deterioration in intercourse satisfaction and orgasm. Additionally, the Ageing Male Symptom (AMS) score, which quantifies hypogonadism symptoms, improved by 7.88 points (p=0.002)[44].

**HYPERTENSION**

The prevalence of hypertension is approximately three times higher in type 2 diabetic men than in non-diabetic patients[45]. Furthermore, the presence of DM was a predictor of new-onset hypertension in the Framingham Offspring Study (OR 3.14; 95% CI 2.1-4.5)[46].

ED can be a consequence and an early marker of hypertension[47]. Hypertension results in endothelial dysfunction (including oxidative stress, cavernosal smooth muscle dysfunction, immune activation, premature vascular ageing and sympathetic activation) which partly explains the association with ED[47].

However, it is also worth noting that several antihypertensive treatments (such as thiazide diuretics and non-selective B-blockers) can adversely affect sexual function[48]. For example, a meta-analysis, conducted in 2002, of 6 RCTs involving 14897 patients demonstrated that beta-blockers slightly

increased significantly per annum the risk of reported sexual dysfunction in 5 per 1000 subjects compared with placebo (95% CI, 2-8)[49].

Thus, one must carefully consider the choice of antihypertensive in patients with diabetes and hypertension. Alternatives such as ACE inhibitors, calcium channel blockers or angiotensin receptor blockers have not been shown to have a detrimental effect on erectile function[48]. Another option is using nebivolol (B1 adrenergic antagonist), which showed higher IIEF scores in every domain function compared to other beta-blockers (eg atenolol, bisoprolol, carvedilol and metoprolol)[50].

**DEPRESSION**

A systematic review of 18 controlled studies (n = 17,399) reported that depression was more likely to be diagnosed in diabetic patients (OR = 2.0, 95%CI 1.8-2.2)[51]. In addition, Wan X et al. performed a systematic review comprising 5 studies (n = 2525) that demonstrated that ED was twice as prevalent in diabetic patients with depression than those without depression (74.2% vs 37.4%). Furthermore, the authors observed three times higher odds of ED in patients with depression (OR 3.08 95% CI 1.32-4.8, P < 0.001, I2 = 83.5%)[52].

Within this context, optimising the psychological status of patients could potentially reduce the psychogenic component of ED. However, there is a paucity of data investigating the therapeutic benefits of treating depression in men with diabetic ED. Moreover, the appropriate selection of antidepressant medications is crucial as some pharmacological agents can cause ED. For example, SSRIs(Selective Serotonin Reuptake Inhibitors) have high rates of sexual dysfunction (reported rates are from 60 to 70%), whereas atypical tricyclic antidepressants have no significant reported effects on sexual dysfunction[53]. Therefore, we recommend both psychiatric counselling and careful selection of medications with titration of dosages[53].

## FAILURE TO RESPOND TO PDE5i

A minimal or absent response to PDE5i is not an uncommon scenario in diabetic patients. Therefore, PDE5i need to be taken appropriately to ensure optimal use, and physicians must consider all the factors modulating the drug's maximum effect (**Table 1**). McCullough et al. studied the impact of counselling on patient satisfaction with sildenafil use in 867 patients with ED. The authors reported that appropriate dose adjustment and tailored instructions increased patient satisfaction by 64%[54]. As a general recommendation, the patient should try PDE5i 6 to 8 times before declaring failure to PDE5i[55].

Furthermore, daily PDE5i might improve rate response in diabetic patients[56]. McMahon et al. showed that patients nonresponding to 20 mg on-demand tadalafil a change to daily tadalafil (10mg) for 12 weeks improved IIEF score up to 8.2 points (P <0.001), 66% achieved successful penetration (P<0.001) and 58% had completed successful intercourse (p <0.001). Diabetes represented 46.4% of the studied population[57]. In addition, daily PDE5i could improve insulin resistance and other glucose metabolic disorders and reduce the risk of cardiovascular events and all-cause mortality; these benefits might be lost if the patient is rapidly escalated to other treatment tiers[58-60].

In a large retrospective study involving 136,306 men from an American database of pharmacy claims, the authors observed that men with diabetes are 60% more likely to require second-line ED treatments within the first 5 years of ED diagnosis than non-diabetic patients (OR 1.6, 95% CI 1.4-1.7). Furthermore, DM patients are twice as likely to require a penile prosthesis insertion compared to non-diabetic men (OR 2.1, 95% CI 1.8-2.6)[61].

The EAU guidelines 2022 advocate that ED management should be tailored to patient expectations, invasiveness, tolerability, and effectiveness[62]. Therefore, DM men should receive a bespoke treatment plan encompassing all evidence-based therapies. It is worth noting that a meta-analysis including 44 studies reported that in men with ED, combination therapies (PDE5I plus other treatments) were associated with a significant improvement in the IIEF score compared to monotherapy with PDE5i alone (Weighted mean difference, 3.02; 95% CI, 1.18-4.87, $I^2$ 77%)[63].

## Treatment modalities to treat erectile dysfunction

## OPTIMISATION OF COMORBIDITIES

Although there is a lack of high-level evidence supporting conservative measures to treat diabetic men who have not responded to PDE5I, it is still worthwhile optimising pre-existing conditions as this may reduce the progression and subsequent complications of individual associated diseases, including premature cardiovascular disease mortality[64]. Thus, many presenting with ED should undergo a multidisciplinary, holistic treatment overview. There are no clinical trials assessing the treatment of depression, hypertension and their impact specifically on erectile function in diabetic patients.

There is also no evidence on the effect of glycaemic treatment in diabetic patients with ED non-responding to PDE5i on the recovery of erectile function; however, a tighter glycaemic control impacts on the prevalence of ED. The Diabetes Control and Complications Trial randomised 761 type 1 diabetic patients to intensive or conventional glycaemic treatment over 10 years and further divided the cohort into primary prevention (recent DM diagnosis without microvascular complications) and secondary intervention (diabetes for 1 to 15 years with microalbuminuria or no proliferative retinopathy)[65].

The primary cohort had a lower prevalence of ED in the intensive group than in the conventional treatment (12.8% vs 30.8%, p = 0.001), and this difference was not seen in the second cohort. Also, the risk of ED in both cohorts was directly linked to mean HbA1C; for every 10% higher HbA1c level, the adjusted odds of ED increased by 21% in the primary cohort (p=0.04) and 55 in the second cohort (p<0.0001)[65].

Weight loss in type 2 diabetic patients has also been proposed to help maintain erectile function. Over a year, 372 patients were randomised to intensive lifestyle interventions vs diabetic support and education to lose weight and increase physical activity. It was observed that erectile function as measured by the IIEF questionnaire in the intensive group worsened by 8%, 70% remained

unchanged, and 22% improved. In contrast, in the comparative group, 20% worsened, 57% remained unchanged, and 23% improved (P = 0.006)[66].

## ANTIOXIDANT SUPPLEMENTATION

A meta-analysis from 2020 compared monotherapy with PDE5i against combined therapy with different antioxidants for ED. It included 9 studies and showed greater improvement in the IIEF score in the combination therapy cohort (weighted mean difference 1.99, 95% CI 1.34 – 2.63, p = 0.01, $I^2$ = 59%)[63]. However, the population was mixed and included diabetic patients and other ED aetiologies, and therefore the applicability of the study's findings to a purely diabetic population is unclear. The antioxidants used included propionyl-L-carnitine, L-carnitine, L-arginine, L-citrulline, transresveratrol, and nicotinic acid[63], and the optimal treatment regimen was unclear. The study outcomes were limited as the heterogeneity of included studies was high.

Some evidence suggests that empiric therapies may have a role in diabetic patients non-responding to PDE5i without causing any serious adverse effects[67-70]. For example, L-arginine is a NO precursor which is therefore necessary for smooth muscle relaxation in the cavernous corpora[71]. Likewise, nicotinic acid is related to energy production in the endothelium and is a vasodilator and thus may improve erectile function [72,73]. Propionyl – L- carnitine (PLC) is an intracellular superoxide scavenger that enhances mitochondrial function, decreases DNA injury, and may improve corporal endothelial functionl[74].

L-arginine has been reported to improve IIEF scores in patients with moderate to severe vasculogenic ED[69]. The role of L-arginine in type 2 DM and ED was assessed in a single centre randomised controlled trial (RCT) including 108 patients. This study showed that in patients with type 2 DM and mild to moderate ED (IIEF-5 scores from 12 to 16), the combination of L-arginine 5 g and tadalafil 10 mg daily for 8 weeks improved IIEF5 scores compared to tadalafil alone (23.5±1.3 vs 20.0±1.4, p < 0.001). A similar outcome was reported in terms percentage change in IIEF-5 scores (82.8%±7.1 vs 62.8%±3.7, p = 0.007)[75].

The addition of PLC to PDE5i may also prove effective in insulin-dependent DM patients not responding to PDE5i[68]. Gentile et al. performed a RCT investigating the effects of PLC and sildenafil compared to PDE5i alone and observed an improvement in the number of successful intercourse attempts in the combination therapy cohort compared to sildenafil alone (76% vs 34%, p < 0.01). Furthermore, the authors reported a statistically significant increase in the IIEF-EF (Erectile Function) score domains in the PLC and sildenafil group compared to the sildenafil group (p <0.01)[69].

Vicari et al. compared the effects of sildenafil 100 mg versus the same dose of sildenafil plus a mixture of antioxidants (Propionyl-L-carnitine + L-arginine + nicotinic acid) in 53 patients with diabetes. The cohort receiving both antioxidants and sildenafil showed a higher response (defined as an increment of 5 points in the IIEF-5 score) than the group receiving sildenafil alone (68% vs 45%, p = <0.05). Similarly, a faster response (time to reach a 5-point increase in the IIEF-5 score) was seen in the sildenafil and antioxidant group compared to the sildenafil group (3 weeks vs 5.2 weeks, P = < 0.05). The response to antioxidants alone was 32%, but a limitation to the study was that no placebo group was included for comparison[76].

A RCT demonstrated that nicotinic acid alone improved significantly the IIEF-EF domain score in patients with moderate (5.28±5.94, p= <0.001) and severe ED (3.31±4.5, p = 0.014) compared to placebo (2.65±5.63, p = < 0.04)[73]. However, no studies have been reported in the diabetic population alone or combined with PDE5i.

## INTRACAVERNOSAL INJECTION THERAPY

The penile injection of erectogenic agents was one of the first available pharmacological treatments for ED, and its early use was described in the 1980s with papaverine and phenoxybenzamine[77]. Nowadays, Intracavernosal injections (ICI) have remained a valuable treatment option in men not responding to PDE5i or where the side effects of PDE5i are not tolerated or contraindicated.

The available Intracavernosal Injections (ICI) formulations are prostaglandin E1 (PGE1) monotherapy, bimix (papaverine 30 mg/mL and phentolamine 1mg/mL), trimix (papaverine 30 mg/mL, phentolamine 1 mg/mL, and PGE1 10 µg/mL) or invicorp (aviptadil 25 µg and phentolamine mesilate 2mg). Although there are few studies specific to the diabetic population, **Table 2** summarises the efficacy of these different treatment options.

A single centre study investigating long-term results of ICI use in 105 patients reported that more than 80% of ICI users did not report complications. The reported adverse effects were plaque formation (10%), mild penile pain (12%), penile curvature less than 30 degrees (10%), bruising (7%), and priapism (7%)[78]. No infections have been reported in non-diabetic patients or purely diabetic populations.

Priapism is a recognised adverse event following intra-cavernosal therapy and defined as an erection lasting more than 4 hours. However, priapism incidence can be as low as 0.5% if patients are well selected and comprehensive education is provided (including training, monitoring, and regular follow up), as demonstrated in a single centre retrospective study comprising 1412 patients enrolled in an ICI program[79].

The dropout rates from ICI have been observed to be from 20% to 70% [79-81]. The dropout reasons reported in a retrospective study of 466 subjects on ICI treatment were suboptimal response (40%), use nuisance (20%), loss of sexual drive (7%), opting for alternative treatments (11%), adverse effects (5.5%) and improvement of spontaneous erections (3%)[80].

Hsiao et al, conducted a retrospective analysis of 122 patients with ED with a median follow up of 25 (±12) months analysing predictors of satisfaction of ICI treatment. A logistic regression analysis showed that higher satisfaction is increased with older patients' age (OR = 2.1, 95% CI 1.6-3.3, p = <0.01), young sexual partners (OR = 2.5, 95% CI 1.4-6.1, p = <0.01), clinically significant increase in the Erectile Function Domain Score (OR = 3.1, 95% CI 2.0-7.1, p = <0.01), and obtaining full rigid erections on the Erection Hardness Scale (OR = 6.8, 95% CI 3.2-19.0, p = <0.001)[81].

A recent case series of 105 subjects have shown that the efficacy and satisfaction with the use of trimix were similar in diabetic compared to non-diabetic men. The comparison between DM and non-DM patients did not show significant differences in the post ICI scores of the IIEF (59.3 vs 60.49,

P = 0.63) and the Erectile Dysfunction Inventory of Treatment Satisfaction (94.0 vs 82.2, P= 0.7)[78]. A significant limitation was the low volume of patients and retrospective nature of the study.

However, Coombs et al. performed a retrospective analysis of a cohort of 1412 patients who had ICI treatment with trimix (84%), bimix (13%) or other agents (1%). The multivariable analysis showed diabetes as a significant predictor for ICI failure (OR 2.9, 95% CI 1.8-4.9, P < 0.5) among other factors such as radical prostatectomy, high trimix dose (>50 units) or > 5-year history of ED[79].

There is evidence that combination therapies with PDE5i and ICI may be an effective treatment modality in diabetic patients. In 2005, a placebo-controlled crossover study assessed the combination of PDE5i (Sildenafil 50 to 100mg) with ICI (alprostadil 20ug bi-weekly) in 40 men who were non-responders to PDE5i alone (20 subjects were diabetic). The combined treatment showed significantly higher (p <0.01) IIEF-Erectile function scores (median 19.4, interquartile range [IQR]10) than sildenafil (median 14, IQR 8.5) or ICI alone (median 10, IQR 6.5). In addition, the authors did not report an increase in adverse events in the combination cohort compared to the monotherapy cohorts [82]. The combination of ICI and PDE5i is a potential therapy for DM men who have failed to PDE5i but with additional risks (although the current evidence suggests this is minimal).

## INTRAURETHRAL/TOPICAL ALPROSTADIL

Synthetic forms of PGE1 have been used as an intraurethral medical therapy for ED treatment and take advantage of the high absorption rate of the urethral mucosa (<10 minutes)[83]. PGE1 causes vasodilation of the erectile tissue and increases cavernosal artery blood flow, thereby facilitating penile erection[83].

The maximum efficacy in terms of the Erection Assessment Score (EAS) is achieved with 1000 μg[84,85]. However, meaningful clinical response (defined as complete rigid erections or sufficient for intercourse) is lower than in ICI, as demonstrated in multiple clinical trials[86-88]. A common adverse effect is penile pain (9 to 18%) without risk of priapism or plaque formation. Regarding discontinuation rates, a systematic review investigating use and barriers of different ED treatments found a dropout rate from 32% to 70%.[89]

Patient acceptance of intraurethral preparations may be higher than ICI due to ease of administration. A RCT involving 60 patients evaluated the self-report ease of use of intraurethral vs ICI preparations, with it being simpler in the former group (90% vs 40%, p < 0.05, respectively)[88].

A retrospective analysis in a single centre involving 82 patients with refractory ED to PDE5i reported that the use of intraurethral preparations could facilitate 62.5% of diabetic patients to have sufficient erections to allow for penetrative sex, compared to patients with hypertension (74%), hypertension + diabetes (65%), and post-radical prostatectomy (58%). In addition, mean IIEF-5 scores increased from 8.3±3.5 to 16.1±4.9 in DM patients. However, when there was severe ED (<7 points in the IIEF-5 score), the response rate (erection sufficient for penetration) decreased to 48%[90].

In general, the combination of intraurethral therapy with PDE5i has shown favourable results in low-quality studies. A retrospective comparative study evaluated the efficacy of combination therapy vs PDE5i alone in patients with ED (n= 65). The IIEF score in the combination treatment was

significantly greater than in the sildenafil monotherapy group (23.1±2.0 vs 19.2±1.8, p <0.05, respectively) and the intraurethral alprostadil group (15.2±1.6, p <0.05).[91].

Although no combination therapy studies have been conducted in a purely diabetic population, in 2020, an open-label, prospective and non-randomised trial studied the efficacy of combination therapy (topical alprostadil + PDE5i) vs PDE5i alone in 170 patients who failed to respond to PDE5i. Diabetic patients were included in both groups (38.9% vs 32.7%, respectively). There was a significant improvement in the IIEF5 scores after treatment in the combination therapy (12.4±3.4 vs 17.1±4.5, p < 0.001) compared to PDE5i alone (12.2±2.5 vs 12.7±3.1, p =0.14). Also, combination therapy had more affirmative answers than monotherapy in SEP (Sexual Encounter Profile) question 2 (78 vs 57; p <0.001) and question 3 (50 vs 1, p <0.001). In addition, no statistical difference was found in adverse effects between the combination and the monotherapy group[92].

## VACUUM ERECTION DEVICES

Vacuum erection devices (VED) increase blood flow into the penile corpora through a soft constriction ring around the penile base generating negative pressure. There are manual or electrical pumps available commercially, and lubricant is applied to enhance sealing.

A study investigating satisfaction with the use of VED in 57 men with ED reported that with appropriate counselling, 96% of the patients were able to maintain erections, 90.7% were able to engage in intercourse, and their female partners reported better sexual experience with the device (83.8%) [93]. Appropriate counselling comprised in-person training, video presentations, live demos, written directions, and discussing realistic expectations[93].

VED should be used for less than 30 minutes to prevent ischemic injury[94]. The side effects reported with VED include penile ecchymoses, penile numbness, anejaculation or painful ejaculation, and skin injury[94]. The contradictions to VED use are priapism, coagulation diseases, and concurrent use of anticoagulation treatment[95].

Combining a VED with PDE5I has been effective in the diabetic population. Sun et al. performed a RCT comparing Sildenafil 100mg plus VED vs VED alone, and the combination cohort had better IEFF scores than VED alone at 1 month (14.86 2.17 vs 12.41±2.6, P <0.0001) and at 3 months (17.5± 2.9 vs 14.2±2.8, p < 0.0001). Also, the combined group had superior successful penetration and intercourse during the same period compared to the monotherapy group. No significant side effects were reported in either group[96].

## PENILE PROSTHESIS

The insertion of a penile prosthesis (IPP) represents an end-stage treatment of ED in diabetic patients as a PP is reserved for refractory cases to ICI or VED, given the potential risks, complications, and irreversibility of the procedure. Comprehensive patient counselling is recommended to ensure appropriate expectations[97].

Both malleable and inflatable prostheses are suitable alternatives in diabetic patients. However, choosing between these options depends on other factors such as the history of retropubic surgeries, pelvic radiotherapy, or manual dexterity.

The optimisation of diabetic control is mandatory before surgery because as poorly controlled diabetes will predispose to prosthetic infection. A multicentre cohort study including 902 patients demonstrated that patients developing a penile prosthesis infection had a higher HBA1c (mean HBA1c of 9.5% vs 7.8%, p <0.001). The authors reported a threshold HBA1c of 8.5% was predictive of infection with an 80% sensitivity and specificity of 65%[98]. However, large randomised controlled trials are needed to confirm the association between hyperglycaemia and infection rates[99].

A meta-analysis comprising 41 non-RCT of 9041 diabetic patients and 36517 non-diabetic patients reported an association with diabetes and penile prosthesis infection (OR 1.53, 95% CI 1.15–20.4, p = 0.004). However, the heterogeneity was high (not reported), and the level of the evidence is low or very low, indicating that the true effect is probably significantly distinct from the estimated effect[100]. Since diabetic men could be considered a high-risk group, it is recommended that high volume surgeons carry out the penile implantation to decrease complication rates and revisions[101].

## NOVEL TREATMENTS

### STEM CELL THERAPY

Stem cells are undifferentiated cells that can differentiate into several cell lineages and are classified depending on their origin and potency. Stems cells have multiple characteristics that could improve ED in diabetic patients, such as differentiation in multiple cell lines, self-regeneration and multiplying capability[102]. Most of the evidence on stem cells regarding ED is based on animal models of diabetic erectile dysfunction where there were improvements in functional and structural changes[103].

A limited number of human studies exist investigating the use of stem cells in DM with ED, but overall, the results are promising. Mirzaei et al. conducted a RCT comprising 20 patients with DM not responding to conventional treatments where autologous mesenchymal stem cells were used. There was a slight significant increase in the IIEF 5 score in the intervention group (baseline 7.2±2.1, 3 months 9.2±3.4, and at 6 months 10.6±4.7) with virtually no changes in the control group (IIEF score 7.2). However, there was no difference in peak systolic velocities and resistive index of the penile vessels in both groups. No complications were reported.[104]

An open-label phase I clinical trial assessing the safety of bone marrow stem cell treatment for erectile dysfunction in 4 diabetic patients with refractory ED found no adverse effects during the 12 months follow up. Secondarily, there was a significant increase in the IIEF-15 score compared to baseline values (p = 0.04) in 3 patients. However, the very low sample hinders any valid clinical utility[105].

Finally, in 2010, Bakth et al. performed a single-blind study with 7 patients with end-stage ED secondary to DM. They used umbilical cord blood stem cells and found that morning erections were

regained in 3 patients within a month, and 2 achieved penetration when PDE5i was used. The total follow up was 9 months.[106]

The limitation to contemporary data is the lack of randomised, controlled trials and the small number of existing studies[105,107,108]. Therefore, until more high-level evidence is available, stem cell therapy in ED should be considered experimental and should only be recommended in clinical trials.

## LOW-INTENSITY EXTRACORPOREAL SHOCK WAVE THERAPY

Low-intensity extracorporeal shock wave therapy (LI-ESWT) delivers low-intensity acoustic energy to the penile corpora resulting in neovascularisation of the erectile tissue, which theoretically should enhance and restore erectile function[109,110]. A meta-analysis including 7 RCT reported an increase in the IIEEF-EF score in men with ED who had LI-ESWT compared to sham groups (MD: 2.54; 95% CI, 0.83-4.25; p= 0.004) [111]. A limitation to the current literature is the lack of consensus regarding the ideal LI-ESWT protocol. However, better outcomes have been reported if more than >18000 total shock waves, 6 weeks length course duration, and a low density of energy[111].

In 2020, a randomised, double-blind sham-controlled trial comprising 40 men with vasculogenic ED refractory to PDE5i demonstrated that LI-ESWT improved IIEF-EF scores in the active group at 3 months follow-up compared to sham groups (median change 3.5, IQR 0-10 vs -0.5, IQR -11-1, p <0.05). However, this difference in the IIEF-score improvement between groups disappeared at the 6-month visit. Also, an Erection Hardness Score > 2 was obtained in 52.5% of the experimental group vs 27.8% in the sham group at 6 months follow up (p<0.05). It is worth noting that diabetic patients represented 30% of each group[102].

Spivak et al. (2019) performed a subgroup analysis of 5 double-blind and sham-controlled trials of LI-ESWT in 350 patients with ED and diabetes. Subjects were divided into PDE5i responders and non-responders. In PDE5i responders, a significant clinical improvement was seen in the IIEF-EF score (defined as an increase of 2, 5 and 7 IIEF-EF points for mild, moderate, and severe ED, respectively) in the treatment group vs sham group throughout the 12-month follow-up. Likewise, the improvement was sustained in 77% and 66% of the patients at 6 and 12 months after the last session, respectively. [112]

Regarding PDE5i non-responders, a significant improvement in IIEF-EF change was seen at 1 month in the experimental group compared to placebo (5.4±5.9, vs -0.5±2, p <0.0001). However, there was a higher increase in the IIEF-EF score in PDE5i responders, that might be explained by more severe ED in the non-responder group. Also, LI-ESWT appears to improve responses to PDE5i even in prior non-responding patients with 55% conversion rates[112].

## LIMITATIONS TO CURRENT LITERATURE AND NEED FOR FUTURE WORK

In summary, the level of evidence of different treatments for treating ED in diabetic men is limited, despite DM being one of the most common comorbidities associated with ED. Therefore, there is a need for further randomised controlled trials investigating the utility of vacuum erection devices, Intracavernosal injections, intraurethral alprostadil, and shockwave therapy in diabetic patients.

However, the current evidence supports the options discussed in this review as clinically safe and comparatively effective in this population. In addition, emerging options such as LI-SWT have promising results in this population. However, stem cell therapy is still not ready for clinical utility and should not be offered outside clinical trials. Therefore, more robust evidence and standardised protocols are needed before its implementation.

## DISCUSSION

Despite the current limitations in contemporary literature, there is still data to support the use of several therapies individually or combined with PDE5i in men who have not responded to PDE5i alone.

The authors recommend the following treatment algorithm for the management of ED in men with DM refractory to PDE5i (**Figure two)**.

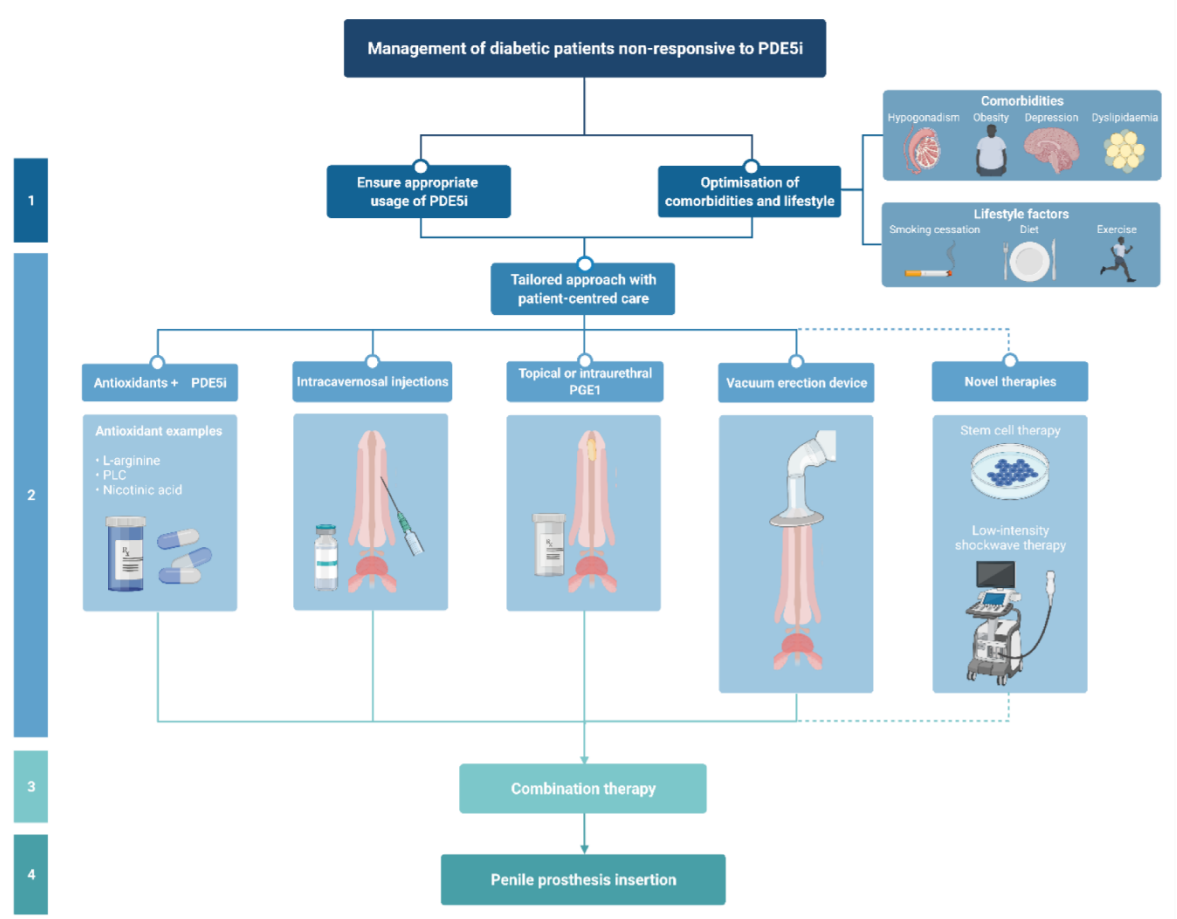



Figure 2. Algorithm of treatment for diabetic patients non-responding to PDE5i.

## CONCLUSION

The quality of the evidence is heterogeneous for diabetic patients not responding to PDE5i. The management of all DM with ED should be holistic and patient-centred with consideration of optimisation of concurrent comorbidities. In those who have not responded to PDE5i, several treatment options can be trialled as an adjunct or alternative therapy to PDE5i. Whilst the use of stem cell therapy and low-intensity shockwave therapy is emerging, randomised controlled trials are required prior to their routine use in clinical practice.

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## TABLES

**Table 1. Checklist to ensure appropriate usage of PDE5i in Diabetic Patients**

- Time to have an effect
- Duration of the effect
- Maximum dose adjustment
- Review of concomitant medications affecting erections
- Need of sexual stimulation
- Counterfeit PDE5i use
- Food and alcohol effects in some PDE5i
- Trial of different PDE5i
- Hypogonadism recognition and hormone replacement therapy

**Table 2. Efficacy of Intracavernosal injection therapies**

| Intracavernosal agent | Population | Dose | Efficacy Response |
|---|---|---|---|
| Prostaglandin E 1[113,114] | Type 1 and 2 DM | PGE1 20 µg<br>Titrated | Full erection 83%<br>Satisfactory sexual activity 76.5 - 93% |
| Bimix[115] | Mixed ED population. DM (27.5%) | Papaverine 30 mg/mL and<br>phentolamine 1 mg/mL | Erection achieved 82.2% |

| | | | |
|---|---|---|---|
| Trimix[79] | Mixed ED population including DM (46%) | Papaverine 30 mg/mL, phentolamine 1 mg/mL, and PGE 1 0 µ g/ mL | Capable of sexual intercourse 89% |
| Invicorp[116] | Non-psychogenic ED | aviptadil 25 µg and phentolamine mesilate 2mg). | Erection suitable for penetration 84% |
| Alprostadil + oral Sildenafil[82] | Mixed ED population. Including DM (50%) Sildenafil non-responders. | Alprostadil 20 µg bi-weekly + 50 mg Oral Sildenafil | Erectile function domain score: 20 (IQR 12.5 – 22.5) * Significantly higher against each therapy and placebo alone |

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