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# Treatment Options for Erectile Dysfunction in Diabetics

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain a penile erection suitable for sexual intercourse. This condition is common with diabetic males. This article comprehensively reviews various treatment options for Erectile Dysfunction (ED) in diabetic men, with a specific focus on the potential of Low-Intensity Extracorporeal Shockwave Therapy (LI-ESWT). Persistent hyperglycemia may decrease nitric oxide (NO) generation, the cycloguanosine monophosphate (cGMP) pathway, reactive free radical levels, the RhoA/Rho kinase pathway, and nerve function, all of which may be contributing factors to ED in diabetic patients. Elevated AGE expression in diabetes individuals' corpus cavernosum may result in structural alterations to the tissue, including thicker arterial walls, decreased flexibility, endothelial dysfunction, and atherosclerosis. Chronic hyperglycemia can produce nerve injury that affects both autonomic and other sensory patterns. The following are existing treatment options for ED; oral phosphodiesterase

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type 5 (PDE5) inhibitor, intracavernosal injection therapy, Intraurethral PGE1 suppository (IUS), Vacuum Erection Device (VED) and penile prosthesis or penile implant. Low-Intensity Extracorporeal Shockwave therapy (LI-ESWT), the treatment options for ED is a non-invasive procedure that focuses on address the root causes of ED. The mechanism underlying the efficacy of shock wave treatment is vasodilation and angiogenesis leading to improved blood flow to the penis by upregulating vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS) and proliferating cell nuclear antigen. The review unveiled the success potential of (LI-ESWT) in treating diabetic impotence.

*Keywords: Diabetes; erectile dysfunction; shockwave therapy.*

## 1. INTRODUCTION

"Diabetes is a medical condition characterized by excessive urine excretion and persistent thirst, often due to a hormonal regulation malfunction. It can be categorized as either diabetes insipidus or diabetes mellitus, with this review focusing on diabetes mellitus (DM). According to the World Health Organization (WHO), DM is a metabolic disorder marked by chronic hyperglycemia. It involves disruptions in carbohydrate, protein, and fat metabolism caused by either absolute or relative insulin deficiency and organ system dysfunction. It typically results from insufficient or ineffective insulin production by the pancreas, leading to fluctuating glucose concentrations in the blood. This condition can have detrimental effects on various body systems, including blood vessels, eyes, kidneys, heart, and nerves" [1].

"Diabetes mellitus is classified into two main types: insulin-dependent diabetes mellitus (IDDM, Type I) and non-insulin-dependent diabetes mellitus (NIDDM, Type II). Type I diabetes is an autoimmune disorder characterized by local inflammation around the islets of Langerhans, followed by the selective destruction of insulin-secreting cells. In contrast, Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion" [1].

"DM is associated with an increased risk of complications, including cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, and amputations" [1]. "In recent years, there has been a significant increase in the prevalence of this disease worldwide, posing financial challenges to governments and NGOs. The International Diabetes Federation (IDF) reported 425 million people with DM globally, with nearly 50% undiagnosed, and a significant portion of these cases in Africa and Asia" (WHO [1]). "In Nigeria, the reported prevalence of DM among adults aged 20–69 years is 1.7%, although this figure is believed to underestimate the true burden of the disease" [1].

"Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain a penile erection suitable for sexual intercourse. The causes of ED range from psychogenic factors such as stress, depression, and anxiety to organic factors. Vasculogenic etiologies involve disorders affecting arterial penile flow or venous outflow. Neurogenic factors include nerve lesions, while iatrogenic factors encompass issues related to pelvic surgery and drug intake" [2]. "n different regions of the world, the prevalence of diabetes mellitus-induced erectile dysfunction (DMED) ranges from 35.8% to 86.1%, and 12% of diabetic patients have ED as the first symptom. The incidence of ED is higher in patients with type 1 diabetes because of more pronounced blood glucose fluctuations. Global research on DMED is expected to increase further. The investigation of the mechanism of DMED and the exploration of new therapeutic means and targets are the focus of future research" [3].

This article comprehensively reviews various treatment options for Erectile Dysfunction (ED) in diabetic men, with a specific focus on the potential of Low-Intensity Extracorporeal Shockwave Therapy (LI-ESWT).

## 2. ERECTILE DYSFUNCTION (ED)

The inability of the penis to sustain or acquire sufficient erection hardness to meet satisfying sexual performance and lasts for longer than three months is known as erectile dysfunction (ED) [4], ED can have a significant impact on a man's quality of life, leading to psychological distress, relationship problems, and decreased self-esteem [5]. Erectile dysfunction can have a range of underlying causes, both physical and psychological. Some of the most common physical causes of ED include: Cardiovascular disease, Neurogenic disorders (diabetic

neuropathy), High blood pressure, High cholesterol, Obesity, Metabolic syndrome, Multiple sclerosis, Parkinson's disease, Peyronie's disease, Prostate cancer, Sleep disorders [5]. Other contributors to erectile dysfunction include; Ageing, surgery kidney disease, Lifestyle (smoking), Covid-19. Hyperglycemia which characteristic in diabetes mellitus leads to the increased expression of advanced glycation end products (AGEs); these AGEs affects the vascular wall of the penile tissues, thereby affecting the diastolic function of the smooth muscle of the penile tissues which in turn leads to diabetic erectile dyfunction [6]. Erectile dysfunction is more prevalent in patients with type 2 DM.

## 3. PATHOGENESIS OF ERECTILE DYSFUNCTION IN DIABETES MELLITUS

“Diabetes mellitus is a metabolic disorder characterized by hyperglycemia brought on by impaired insulin secretion, impaired insulin action, or both [7]. Persistent high blood sugar levels can cause heart, brain, and circulation problems as well as death” [8]. “Diabetes is regarded as a key risk factor for ED. Persistent hyperglycemia may decrease nitric oxide (NO) generation, the cycloguanosine monophosphate (cGMP) pathway, reactive free radical levels, the RhoA/Rho kinase pathway, and nerve function, all of which may be contributing factors to ED in diabetic patients” [9]. “Advanced glycation end products (AGEs), the byproducts of amino non-enzymatic glycation of proteins, lipids, and nucleic acids in human tissues, will rise while hyperglycemia persists in the body. Elevated AGE expression in diabetes individuals' corpus cavernosum may result in structural alterations to the tissue, including thicker arterial walls, decreased flexibility, endothelial dysfunction, and atherosclerosis. This process may result in overloaded peroxynitrite, which may cause oxidative harm to several significant biomolecules and result in ED” [10]. “The cGMP primarily causes the relaxation of cavernosal vascular smooth muscle by altering the levels of intracellular and extracellular calcium and calcium and potassium ions. Certain literature reviews suggest that the loss of cGMP and the poor relaxation of cavernosal smooth muscle caused by the oxygen free radicals produced by AGEs-induced associated cellular oxidative damage and the quenching of NO contribute to the development of ED in people with diabetes” [11]. “Chronic hyperglycemia can produce nerve injury that affects both autonomic and other sensory patterns” [12]. “Patients with diabetes and ED sometimes have low levels of testosterone in the morning” [13]. “It is important to recognize other conditions that can affect testosterone levels, such as endocrine disorders and diseases of the urinary system, as diabetes is not the only condition that can cause low testosterone levels” [14,6].

## 4. TREATMENT OF ERECTILE DYSFUNCTION

### 4.1 Oral Phosphodiesterase-5(PDE5) Inhibitors

Phosphodiesterase type 5 (PDE 5) is an enzyme found in smooth muscle, platelets and the corpus cavernosum. The oral phosphodiesterase type 5 (PDE5) inhibitor class is a mainstay of ED treatment. Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra) are the four main PDE5 inhibitors. Viagra received Food and Drug Administration (FDA) approval in 1998 and became the first oral therapy for ED. The development of alternative PDE5 inhibitor medicines led to the approval of Cialis (2003), Levitra (2003), and Stendra (2012) for the treatment of ED.

“These medications raise the levels of intracellular cyclic guanosine monophosphate (cGMP) in cavernous tissue, which relaxes trabecular and arterial smooth muscle and increases arterial inflow and penile erection rigidity” [15]. **“**The relaxation of corpus cavernosum smooth muscles is not directly impacted by PDE5 inhibitors. Hence, for an erection to occur after ingestion, there must be sufficient sexual stimulation” [15]. **“**The mean time to maximum plasma concentration of avanafil is within 0.5-0.75 hours, sildenafil and vardenafil is 1 hour and for tadalafil is 2 hours, while the half-lives of sildenafil and vardenafil are 4 hours, avanafil is 5 hours and that of tadalafil is 17.5 hours. Food high in fat delays and reduces the absorption of sildenafil, avanafil and vardenafil, but does not affect the rate or extent of absorption of tadalafil” [15]. “These pharmacokinetics give tadalafil the advantage of allowing spontaneity in sex and giving the couple an open window for successful intercourse, making it different from the other three PDE5 inhibitors. PDE5Is are effective in non-diabetic men to a degree of 60% to 70%” [15]. **“**However, efficacy is lower in diabetic men due to impaired endothelium-derived factors in penile arteries

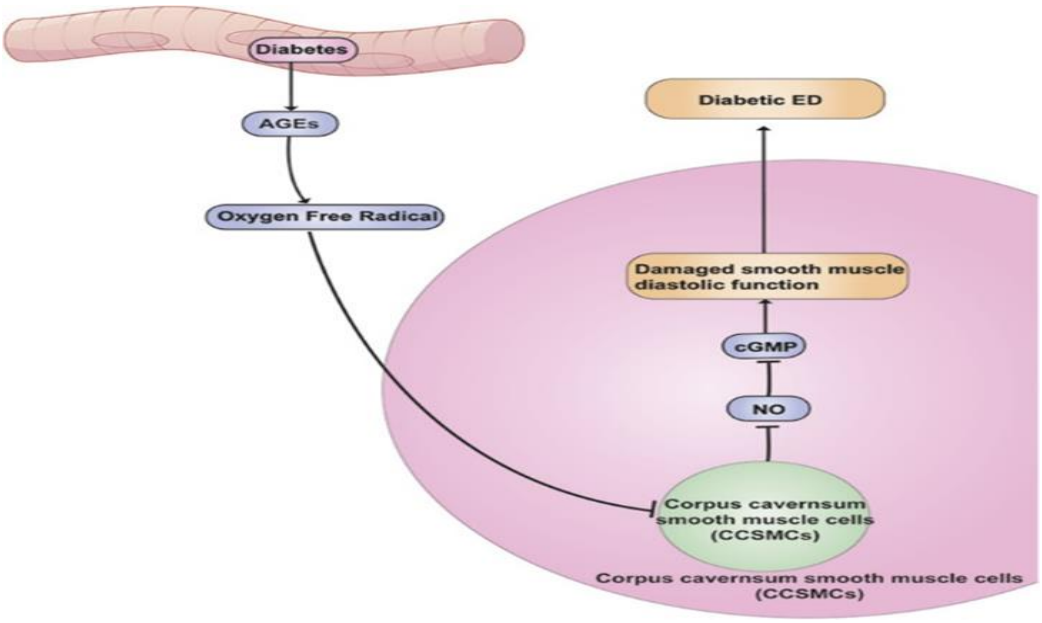


**Fig. 1. Treatment of Erectile dysfunction Pang et al. [15]**

and underlying endothelial dysfunction. This may explain why ED is more refractory to treatment in diabetic men. Five preference experiments comparing tadalafil and sildenafil revealed an overall preference for tadalafil based on a longer duration of action, according to a 2009 assessment of seven preference trials" [15]. **"**Patients receiving sildenafil or vardenafil were substantially more likely to switch prescriptions than those taking tadalafil in a 6-month observational research, tadalafil consistently outperforms sildenafil or vardenafil in trials of patient preference. The fact that tadalafil may be taken with fatty foods without affecting bioavailability, unlike sildenafil or vardenafil, may be one of the favored considerations; The minor preference for tadalafil may potentially be influenced by longer duration of action for up to 36 hours from just a single dose and more spontaneity in sexual activity" [14]. Similar efficacy and safety concerns have been demonstrated for avanafil as well as the other three main PDE5 inhibitors. But avanafil's rapid onset of effect sets it apart from other medications. Common side effects of PDE5Is are; Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, except sildenafil's visual abnormalities and tadalafil's back pain. It is not advised to utilize any organic nitrates concurrently, such as amyl nitrite, isosorbide mononitrate, or dinitrate, or sublingual nitroglycerin. Due to the varied half-lives of the medications, nitroglycerin must be avoided for at least 24 hours after the last dose of sildenafil or vardenafil, 48 hours after the last dose of tadalafil, and 12 hours after the last dose of avanafil [14].

## 5. INTRACAVERNOSAL INJECTION (ICI)

Before the widespread use of PDE5 inhibitors, intracavernosal injection therapy was a well-recognized treatment for ED introduced in 1983 with a high success rate of efficacy [14]. ICI therapy is still a significant second-line option for the treatment of ED in individuals with contraindications, substantial side effects, or inadequate responses to the first-line treatment even in the era of PDE5 inhibitors. ICI is a procedure that involves inserting a tiny needle directly into the corpus cavernosum at the lateral base of the penis to administer vasoactive medications. Among these vasoactive drugs are phentolamine, papaverine, and Prostaglandin E1 (PGE 1) (alprostadil) [16]. These drugs can be combined with one or more additional medications in a formula or taken as a PGE1 monotherapy (bi-mix of papaverine and phentolamine; tri-mix of prostaglandin E1, papaverine, and phentolamine). The medication causes relaxation of the smooth muscle cells and increases blood flow to the penis, resulting in an erection. PGE 1(alprostadil) medication is most commonly used for this purpose; as part of its mode of action, it binds to G proteins linked to PGE1 receptors on the surface of smooth muscle cells, activating the cyclic adenosine monophosphate (cAMP) pathway and causing

vascular smooth muscle relaxation and erection. ICI is a successful local medication therapy for ED, and patients' unique situations and needs can be taken into account when creating tailored treatment programs [17]. Several vasoactive medications combined with various injection dosages can greatly enhance the therapeutic efficacy and lessen side effects. According to the study, patients who received injections of prostaglandin E1 plus papaverine were better able to attain sufficient erectile function than those who received injections of prostaglandin E1 alone [17]. In a retrospective analysis, the researcher included 105 middle-aged and older patients and discovered that after ICI treatment, the patient's penile hardness increased, erectile function improved, and there were no visible consequences, proving the safety and viability of ICI therapy [18]. Nonetheless, the clinical usage of ICI has, however, gradually diminished as a result of the use of PDE5Is because it has a high dropout rate and is connected to priapism, ecchymosis, hematomas, and penile fibrosis [18].

## 6. Intraurethral PGE1 SUPPOSITORY (IUS)

“Intraurethral PGE1 suppository (IUS) uses a small intraurethral delivery catheter to place a PGE1 within the urethra for absorption through the corpus cavernosum before sexual intercourse. The most popular agent is alprostadil (PGE1) used in a urethral suppository first marketed as MUSE (Medicated Urethral System for Erection). MUSE comes in the form of a pellet suspended in polyethylene glycol and is administered with an applicator. The vasoactive agent is absorbed through the urethra (about 80 % in 10 min) and facilitates erection. This is similar to alprostadil ICI, but is less invasive and less effective than ICI” [18]. This route of administration may be preferred in patients who are poor responders, are contraindicated for oral medication, or have fear of injectable medications. Constraints include warnings against sexual activity and engaging in sex without using a condom with a pregnant woman. Other contraindications include urethral abnormalities, urethritis, and predisposing hematological diseases like thrombosis or hyper-viscosity syndrome that could cause priapism. Adverse effects include; Penile pain, urethral burning (greater than 10%), dizziness, headache, pain in the central nervous system, testicular pain, minor urethral bleeding, leg pain, perineal pain, and tachycardia (less than 2%) are among the side effects of this medication.

## 7. VACUUM ERECTION DEVICE (VED)

VED is a mechanical device which consist of a shrink ring, a cylinder and a pump powered manually or by battery power [19]. A negative pressure is created around the penis in EDs, which causes blood to flow into the corpora cavernosa (the two main chambers of the penis). By putting a cylindrical piece of plastic over the penis and using a hand-held pump to create a vacuum, negative pressure is produced. This makes the penis erect by drawing blood into it. The erection is then maintained by stopping blood from leaking out by placing a constriction band around the base of the penis. VED has a good success rate and little negative effects, and it is mostly used to treat individuals with organic ED [20]. 56 middle-aged and senior patients with ED were treated with VED in a recent study; 96% of the patients thought the device may improve erection ability and 94% of patients and their partners reported having satisfying sexual activities again. However, nearly 28.6% of the patients reported experiencing physical discomfort while using the device, typically as a result of the discomfort brought on by wearing the restraint ring [19]. Penile contusion from improper use, particularly in patients taking or recently taking anticoagulants, penile numbness and/or pain, penile coldness, and ejaculatory issues are only a few of the frequent side effects of VEDs. The patient may experience some psychological distress as a result of the device, such as frustration and a sense of being powerless.

## 8. PENILE PROSTHESIS

A penile prosthesis or penile implant is another treatment option for men with erectile dysfunction. Penile prosthesis surgery involves placing a prosthetic device inside the penis and scrotum. This device helps men with erectile dysfunction achieve an erection and regain sexual function. These devices are either malleable (semi-rigid) or inflatable.

- Malleable penile prosthesis; the non-inflatable or semi-rigid malleable penile prosthesis consists of two rods that are inserted into the penis corpus. The rods are hard but malleable in that they may be manually bent into an erect position [21]. There are two different kinds of malleable implants: one consisting of silicone and without an internal rod, commonly known as soft implants; the other has an internal

silver or steel spiral wire core wrapped in silicone. Several of the models feature tails that can be cut to a different length [19].

- Inflatable penile prosthesis; the more recently created inflatable penile implant (IPP) consists of a collection of inflated cylinders and a pump mechanism. There are two types of inflatable penile implants: two-piece and three-piece IPPs, based on structural variations. Both varieties of inflatable devices have cylinders that are pumped with sterile saline solution when they are being filled. The penis's cavernous body is where the cylinders are placed. The cylinders are connected to the pump system, which is then positioned in the scrotum [19]. A separate sizable reservoir is attached to the pump in three-piece implants. Although the reservoir is typically positioned in the retro pubic region (Retzius' space), alternate positions, such as between the transverse and rectus muscles, have also been mentioned in some studies. The firmness and girth of the penis that three-piece implants offer are more appealing and resemble a natural erection. Moreover, three-piece implants offer full penile flaccidity when deflated due to the existence of a huge reservoir, providing greater comfort than two-piece inflatable and malleable implants [19]. In order to replace the non- or minimally functional erectile tissue, saline solution is manually pumped from the reservoir into bilateral chambers of cylinders implanted in the shaft of the penis. An erection results as a result. The AMS 700 Penile Implant is the #1 physician-preferred inflatable prosthesis designed to treat ED, it most closely mimics a natural erection, provides rigidity when inflated and a natural, flaccid appearance when deflated. The overall satisfaction rate with penile implants reaches over 90%. Both self and partner-reported satisfaction rates are evaluated to assess the outcomes. It has been shown that implantation of inflatable penile prosthesis brings more patient and partner satisfaction than medication therapy with PDE5 inhibitors or intracavernosal injections [22]. Satisfaction rates are reported to be higher with inflatable rather than malleable implants. Nevertheless, PPI is costly, traumatic, and prone to complications, such as prosthetic infection, pump migration, automatic inflation, secondary surgery, etc. This is the main reason why it cannot become a first-line treatment [22].

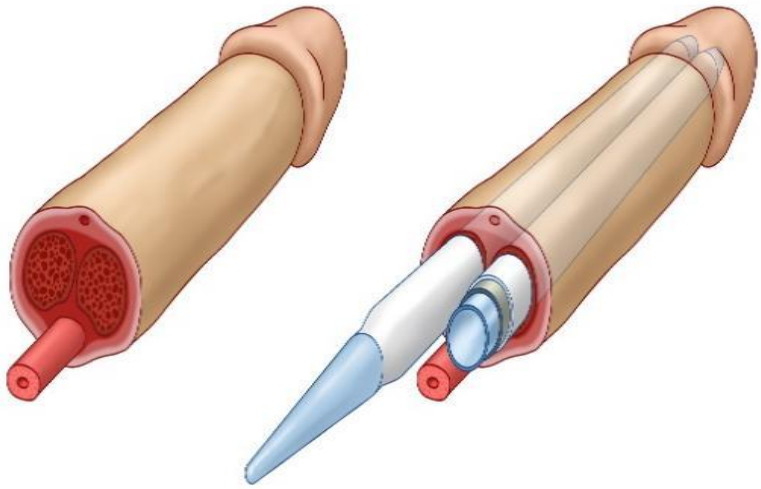

**Fig. 2. A diagram of an inflatable penile implant inserted into corpus cavernosum of the penis Penile implant [23]**

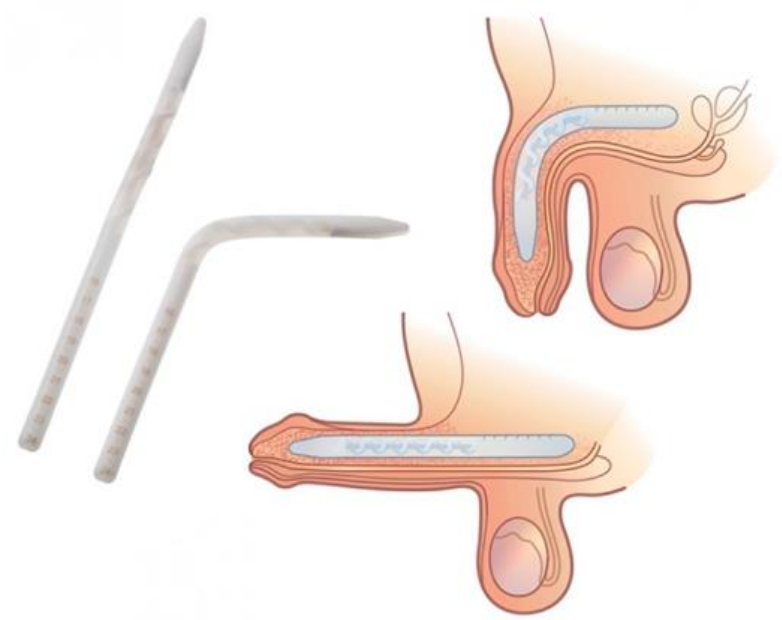

**Fig. 3. A diagram of a Malleable penile prosthesis Penile Implant, n.d. [24]**

## 9. NEW MANAGEMENT USING LOW-INTENSITY EXTRACORPOREAL SHOCKWAVE THERAPY

These old treatments for erectile dysfunction are very effective and are reasonably safe with unwanted or adverse side effects and contraindications, they do not alter the underlying physiology of the erectile mechanism, these treatments are usually taken on demand, prior to the sexual act and their effect is essentially time limited. A treatment for men with ED that is rehabilitative or perhaps curative and enables them to restore spontaneous sexual activity with normal intimacy and without side effects is an unmet medical goal. The majority of ED patients depend on their treatment to preserve their sexual function. Current evidence from numerous trials suggests that corpora cavernosa low-intensity extracorporeal shockwave therapy (LI-ESWT) could likely achieve this goal [22].

Shockwaves (SWs) are acoustic waves that convey energy and can be non-invasively targeted and concentrated to effect a distant, chosen anatomical region when they are traveling through a material. Shockwaves are generated by a hand device outside of the body (extracorporeally) and then travel through the patient‘s skin into the damaged or diseased tissue. This is why the method is called Extracorporeal Shockwave Therapy or ESWT for short. There are two types of shockwaves, Radial and Focused. Radial shockwaves should not be used for ED.

- Radial Shockwaves (Soft shock) are used to treat larger and more superficial indications.
- Focused Shockwaves (Hard shock) have a smaller more targeted focal point for greater accuracy and greater treatment depth. The smaller targeted treatment area allows for a more comfortable treatment and is therefore used for the treatment of men’s sexual health conditions.

It was originally introduced as a non-invasive treatment for kidney stones and has since been used in the management of many other conditions, including bone fractures, musculoskeletal disorders, wound healing, Peyronie’s disease, and ischemic cardiovascular disorders. In 2010, it was proposed that low-intensity extracorporeal shockwave therapy (Li-ESWT) could be a promising new treatment option for erectile dysfunction (ED) [22]. A physical shock wave known as a low-intensity extracorporeal shock wave (Li-ESW) is a non-invasive emits energy at a density of less than 0.1 mJ/mm2. Li-ESWT concentrates on the target tissue area through the sound wave travelling through the tissue structure as a non-invasive therapy technology [25].

The mechanism underlying the efficacy of shock wave treatment is vasodilation and angiogenesis

leading to improved blood flow to the penis. When LI-ESWT is employed on an organ, the relatively weak but focused shockwaves interact with the deep tissues that are being targeted, causing micro trauma and mechanical stress. This stress and micro trauma, also known as shear stress, causes a series of biological processes that produce angiogenic factors, such as vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS), proliferating cell nuclear antigen, to cause the tissue to neovascularize and enhance its blood supply [26]. Outcome measures used are changes in the International Index of Erectile Function-erectile function domain (IIEF-ED) scores, the EHS measurement, the minimal clinically important difference (MCID) of IIEF better assesses the true clinical efficacy of LI-ESWT.

Vardi et al., (2010) evaluated IIEF at 1 month following LI-ESWT and found that the IIEF did not significantly increase (MD: 0.37; 95%CI, 1.45 to 2.19; p = 0.69). Twenty middle-aged patients with vascular ED were given 12 Li-ESW treatments over the course of six weeks by Vardi et al., (2010). The findings showed that 75% of patients had significantly enhanced erectile function, and the IIEF score was obviously higher as well. The patient's penile blood flow, erection duration, and penile hardness were also improved. However, studies that evaluated the IIEF 3 months after therapy discovered a substantial rise (MD: 2.71; 95% CI, 1.51-3.91; p 0.0001) in the IIEF. Moreover, Li-ESW therapy has been demonstrated to be a secure and efficient treatment option for individuals with suboptimal PDE5I effects [27]. According to a study, using Li-ESW can make PDE5I tolerance go away and help more than 50% of patients reach adequate erectile rigidity [28].

## 10. EFFECT ON VASCULAR ENDOTHELIAL GROWTH FACTOR

A significant angiogenic agent that promotes the growth of new blood vessels, which increases blood flow into the target tissues. Several investigations that examined how Li-ESWT affected the expression of VEGF in penile tissues revealed a considerable rise in VEGF levels and sustained effect of VEGF expression following treatment. A systematic review examining the effects of LI-ESWT in diabetic males found that treated individuals penile tissues significantly increased VEGF expression [29]. VEGF has a significant role in the regeneration of penile tissues and restoration of erectile function in addition to angiogenesis.It has been demonstrated that LI-ESWT induced elevation of VEGF enhances smooth muscle and endothelial cell proliferation , resulting in enhanced vascular and erectile fuction.( in the management of postprostatectomy (ED).

## 11. EFFECT ON ENDOTHELIAL NITRIC OXIDE SYNTHASE (eNOS)

Nitric oxide (NO), a signalling molecule that induces vasodilation and increased blood flow, is synthesized by the enzyme eNOS [30]. NO relaxes the smooth muscle cells in the penile arteries and increases blood flow to the corpus cavernosum, causing penile tumescence [31]. LI-ESWT can increase ENOS expression and NO generation in the penile tissue, leading to improved erectile function. A review showed that LI-ESWT was effective in enhancing erectile function in males with postprostatectomy ED and this improvement was associated with elevated eNOS expression [32-34].

## 12. CONCLUSION

The use of LI-ESWT as an ED treatment has received a lot of interest. The number of studies on this subject has dramatically expanded, and the majority of these studies have shown optimistic findings, like improved IIEF and EHS and an impact that lasts up to three months. This review has shown that LI-ESWT restores to a greater percentage the erectile function in men with diabetic erectile dysfunction by increasing vasodilation and promoting angiogeneis. LI-ESWT has also shown potentialof turning non-responders of oral PDE-5 Inhibitors therapy to responders.

Therefore, diabetic erectile dysfunction could consider LI-ESWT as treatment option when other conventional treatments (oral agents) have proven to be unsuccessful.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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