# The Role of Low-Intensity Extracorporeal Shockwave Therapy (LI-ESWT) in the Management of Erectile Dysfunction.

***Essay***

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***By***


## Ahmed Abdelsalam Saadoun Ismaael

**M.B.B.CH of Surgery and Medicine**
**Faculty of Medicine, Ain-ShamsUniversity**


***Under Supervision of***


## Prof.Dr.Mohammed Tarek Mohammed Fathy Zaher

**Professor of Urology**
**Faculty of Medicine, Ain-ShamsUniversity**

## Dr. Mohammed Ahmed Gamal Eldin

**Lecture of Urology**
**Faculty of Medicine, Ain-Shams University**



**Faculty of Medicine**
**Ain-Shams University**

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*Ahmed Abdelsalam Saadoun Ismaael*

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# List of Abbreviations

| | |
|---|---|
| **ADMA** | **Asymmetric Di-Methyl L-Arginine** |
| **c-GMP** | Cyclic Quanosine Monophosphate |
| **CGRP** | Calcitonin Gene Related Peptide |
| **CPCs** | Circulating Progenitor Cells |
| **CPPS** | Chronic Pelvic Pain Syndrome |
| **CNS** | Central Nervous System |
| **CVOD** | Corporal Veno-Occlusive Dysfunction |
| **CYP34A** | Cytochrome P450 3A4 |
| **DICC** | Dynamic Infusion Cavernosometry and Cavernosography |
| **DM** | Diabetes Mellitus |
| **EAU** | European Association of Urology |
| **ED** | Erectile Dysfunction |
| **EDSWT** | Erectile Dysfunction Shock Wave Therapy |
| **EFD** | Energy Flux Density |
| **EMA** | European Medicines Agency |
| **EnF** | Endothelial Function |
| **eNOS** | Endothelial Nitric Oxide Synthase |
| **ESWT** | Extracorporeal Shock Wave Therapy |
| **ETs** | Endothelins |
| **FMDs** | Flow-Mediated Dilatation techniques |
| **HUVECs** | Human Umbilical Vein Endothelial Cells |
| **ICI** | Intra-Cavernosal Injection |
| **IF** | Immuno-Fluorescent |
| **IIEF** | International Index for Erectile Function |
| **INF** | Infliximab |
| **LI-ESWT** | Low-Intensity Extracorporeal Shockwave Therapy |
| **L-NMMA** | L-Nitro Mono-Methyl L-Arginine |
| **LV** | Left Ventricular |
| **MPa** | Mega Pascals |
| **MPOA** | Medial preoptic area |

| | |
|---|---|
| **MSCs** | Mesechymal Stem Cells |
| **NA** | Noradrenaline |
| **NAD** | Nicotinamide Adenine Dinucleotide |
| **NADPH** | Nicotinamide Adenine Dinucleotide Phosphate |
| **NANC** | Noradrenergic Non-Cholinergic |
| **NIH** | National Institutes of Health |
| **NO** | Nitric Oxide |
| **NO-cGMP** | Nitric Oxide-cyclic GuanosineMonophosphate |
| **NOS** | Nitric Oxide Synthase |
| **NPT** | Nocturnal Penile Tumescence |
| **NPTR** | Nocturnal Penile Tumescence and Rigidity |
| **NS** | Nerve Sparing |
| **OZR** | Obese Zucker Rats |
| **PCNA** | Proliferating Cell Nuclear Antigen |
| **PDE5Is** | Phosphodiesterase 5 Inhibitors |
| **PGE** | Prostaglandins |
| **PSA** | Prostate Specific Antigen |
| **RAGE** | Receptor for advanced glycation end products |
| **RP** | Radical Prostatectomy |
| **SHR** | Spontaneously Hypertensive Rats |
| **SMCs** | Smooth Muscle Cells |
| **STZ** | Streptozotocin |
| **SWA** | Shockwave Applicator |
| **TGF** | Transforming Growth Factor |
| **TGF-â1** | Transforming Growth Factor Beta 1 |
| **TNF** | Tumour Necrosis Factor |
| **VEDs** | Vacuum Erection Devices |
| **VEGF** | Vascular Endothelial Growth Factor |
| **VIP** | Vasoactive Intestinal Peptide |
| **VSMCs** | Vascular Smooth Muscle Cells |
| **vWF** | von willbrand factor |

# Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection of sufficient quality to permit satisfactory sexual intercourse **[1]**.

ED can have a significant impact on the physical and psychosocial health aspects of men and their partners, as evidenced by the large volume of publications on male sexual dysfunction. The development of ED is frequently attributable to both psychogenic factors as well as physiological alterations of neural, vascular, hormonal and endothelial function **[2]**.

A recent international consultation collaborative study reported that the prevalence of erectile dysfunction increases in men as age increase, and an estimated 20-30% of adult men between 40 and 70 years of age suffered from at least one episode of sexual dysfunction **[3].**

Age related erectile dysfunction is primarily because of corporal veno-occlusive dysfunction [CVOD]; as the result of a loss of the corporal smooth muscle cells [SMCs] together with excessive collagen deposition within the corpora **[4]**.

On the other hand , loss of cavernous nerve function is primary responsible for the development of erectile dysfunction [ED] after pelvic surgery and acts as the primary target for potential neuroprotective or regenerative strategies and emerging neuromodulatory molecules for the treatment of neurogenic erectile dysfunction caused by cavernous nerve injury **[5]**.

Distinguishing whether the cause of erectile dysfunction is predominantly organic or psychological may be useful in directing management **[6].**

In the past decade, phosphodiesterase 5 inhibitors (PDE5-Is) have become available for the treatment of erectile dysfunction (ED). However, their effect is still limited to the sexual act and probably do not improve spontaneous erections. These limitations are probably due to their inability to improve penile blood flow for a time period that is sufficient to allow optimal oxygenation and recovery of cavernosal vasculature. Recently, the effect of long-term daily use of PDE5-Is on endothelial function (EnF) has been shown to induce a short-term improvement in erectile function but probably not a longstanding one **[7].**

In the search for a new treatment modality that would provide a rehabilitative or curative effect for ED, we looked into technologies that could potentially affect endothelial function and improve penile hemodynamics. We came across some related preliminary publications, particularly from the cardiovascular literature, showing that in vitro as well as in vivo (porcine model) low-intensity extracorporeal shockwave therapy (LI-ESWT) could enhance the expression of vascular endothelial growth factor (VEGF) and its receptor Flt-1 **[8]** and induce neovascularization and improve myocardial ischemia. Newer studies further demonstrated this hemodynamic effect in humans **[9].**

Moreover, LI-ESWT was found to be effective not only in the myocardium, but also in other organs with impaired vascularity. Recently, this treatment modality using LI-ESWT was found effective in the treatment of chronic diabetic foot

ulcers as compared with hyperbaric oxygen therapy, showing better clinical results and local perfusion **[10].**

In a prospective randomized trial, LI-ESWT was also effective in improving wound healing after vein harvesting for coronary artery bypass graft surgery**[11].**

The mechanism of action of LI-ESWT is still unclear. It has been shown that this low intensity energy induces non-enzymatic production of physiologic amounts of nitric oxide, and activates a cascade of intracellular signaling pathways that lead to the release of angiogenic factors. These encouraging experimental and clinical outcomes provided the theoretic basis for applying this treatment modality to cavernosal tissue in order to improve penile vascular supply and EnF in men with longstanding vasculogenic ED.

# Aim of the work

This essay will focus on the role of low intensity extracorporeal shockwave therapy (LI-ESWT) in the management of male erectile dysfunction [ED], as regards to efficacy, and outcome.