

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

Essay

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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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	Mesenchymal 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 Guanosine Monophosphate
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-β1	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.