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Department of Urology, Juntendo University Urayasu Hospital, Tokyo, Japan Interests: Testosterone; LOH; Male infertility; Sexual function; Prostate



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Penn Medicine, Perelman School of Medicine, University of Pennsylvania Health System, Perelman Center for Advanced Medicine, Philadelphia, PA, USA Interests: Bladder cancer; Urology; Prostate cancer



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Department of Internal Medicina, School of Medicine, Federal University of Goias, Goiania, Brazil Interests: Chronic diseases; Primary care; Multimorbidity; Health systems research



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Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy Interests: Penile prosthesis; Peyronie'disease – surgery; Gender reassignement surgery



#### Rocco Salvatore Calabro, MD, PhD IRCCS Centro Neurolesi Bonino-Pulejo, Neurorehabilitation University, Messina, Italy Interests: Robol-aided neurorehabilitation; Disorders of consciousness; Neurosexology



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#### Francesco Cantiello, MD, PhD

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Interests: new imaging methods; such as mpMRI and PET/CT; and new urinary and serum biomarkers in diagnosis; staging and re-staging of prostate cancer; impact of metabolic syndrome and each single metabolic components on onset and progression of benign prostatic hyperplasia and urological cancers; new serum and hematopoietic markers on superficial bladder cancer



#### Daniel Castillo, PhD

Department of Didactics of Musical, Plastic and Corporal Expression, Faculty of Education, University of Valladolid, Soria, Spain Interests: new technologies; team sports; physical education; physical activity; health; soccer



## Eric Chung, PhD

Department of Urology, Princess Alexandra Hospital, University of Queensland, and AndroUrology Centre, Brisbane, QLD, Australia Interests: Penile and urinary reconstructive and prosthesis surgery; Andrology (male sexual and reproductive medicine); Voiding dysfunction; Ageing male



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Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy Interests: Male infertility

# Jø.

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Faculty of Medicine, Department of Psychiatry, Geneva University (UNIGE), Geneva, Switzerland, Faculty of Medicine, Department of Biomedical Sciences, Swiss Italian University (USI), Lugano, Switzerland Interests: suicide; emergency psychiatry



#### Kelvin Davies, PhD

Department of Urology, Department of Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY, USA

Interests: Basic Science of Sexual Medicine (1) investigating mechanisms to facilitate cavernous/peripheral nerve regeneration as a treatment to erectile dysfunction following radical prostatectomy (2) the use of nanoparticles as a dermal delivery vehicle for various agents used to treat urogenital disease (3) the role of the MaxiK channel expressed in the urothelium in regulating overall bladder activity (4) the molecular mechanisms underlying the development of priapism associated with sickle cell disease (5) the role of the microbiome in the development of kidney stone disease and (6) the role of opiorphin in sperm motility (7) the mechanism of hyperglycemic memory in the diabetic bladder



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Clinica Medica Unit, Azienda Ospedaliero-Universitaria, University of Ferrara, Cona, Italy

Interests: Internal medicine; Emergency medicine; Cardiovascular disease; Dyslipidemia



#### Andrea Garolla, PhD

Unit of Andrology and Reproductive Medicine, Department of Medicine, University of Padova, Padua, Italy

Interests: Male reproduction and male infertility; Male sexual dysfunctions and disorders; Sexual transmittable diseases; Male HPV; Hypogonadism; Male osteoporosis



#### Badicu Georgian, MD

Transilvania University of Brasov, Faculty of Physical Education and Mountain Sports, Department of Physical Education and Special Motricity Interests: Physical activity; Fitness; Education; Obesity; Diet; Well-being; Recreation; Football; Public health; Quality of life; Sports activities; Physical education; Didactic of physical education and sports; Sleep Special Issues and Topics in IMR Press journals

Special Issue in Exercise and sports in men: from health to sports performance



#### Igor Grabovac, MD, PhD

Department of Social and Preventive Medicine, Center for Public Health, Medical University of Vienna, Vienna, Austria

Interests: health behaviour; health behaviour modification; monitoring and prevention of HIV/AIDS; addiction and mental health issues among PLWHIV; primary prevention; issues of sexual and gender diversity; occupational medicine and health at work; issues of healthy aging

Special Issues and Topics in IMR Press journals Special Issue in Cancer Prevention in Men



#### Antonio Hernández-Mendo, PhD

Departamento de Psicología Social, T.S., A.S. y E.A.O, Universidad de Málaga, Málaga, España

Interests: sport psychology; engagement in elite youth athletes; qualitative analysis; sports science; data analysis; methodology; assessment; exercise science; statistical analysis; exercise physiology; psychological assessment; biomechanics



#### Chee Kong (Christopher) Ho, MD

School of Medicine, Taylor's University, Kuala Lumpur, Malaysia Interests: Andrology; Men's health; Endourology



## Sung Kyu Hong, MD, PhD

Department of Urology, Seoul National University College of Medicine, Seoul, Republic of Korea/Seoul National University Bundang Hospital, Seoul, Republic of Korea Interests: prostate cancer; robotic surgery



## Ji-Sien (William ) Huang, MD, PhD

Department of Urology, Taipei Veterans General Hospital, Taiwan; Department of Urology, Department of Physiology, College of Medicine, National Yang Ming Chiao Tung University, Taiwan Interests: Andrology; Male infertility; Reproductive endocrinology



### Hyunsik Kang, PhD

College of Sport Science, Sungkyunkwan University, Suwon, Republic of Korea

Interests: relationships of lifestyle risk factors and mental health issues such as cognitive impairment/dement and anxiety/depression; therapeutic roles of adopting a healthy lifestyle (including physical activity and fitness and nutrition) against mental health risk; molecular mechanisms underlying exercise training-induced health benefits for mental health conditions

Special Issues and Topics in IMR Press journals Special Issue in Lifestyle Risk Factors and Mental Health in Older Men



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Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA Interests: Prostate and bladder cancer; Male and female sexual dysfunction



#### Jung-hoon Lee, PhD

Department of Physical Therapy, Dong-eui University, Busan, Republic of Korea

Interests: Rehabilitation and physiotherapy for musculoskeletal dosorders; Kinesiology taping; Cross taping; Balance control; Nerve entrapment syndrome; Othosis for misalignment; Measurement and evaluation



#### Myeong Soo Lee, PhD

KM Science Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

Interests: Evidence-based medicine for CAM (systematic review and meta-analysis); Standardization of diagnosis tool in traditional medicine; Clinical investigation of complementary therapies; Developing clinical practice guideline in traditional medicine; Objectifying the assessment of various diseases with oriental medical tools; Psycho-neuro-immunological effects of CAM (specifically qigong, tai chi, acupuncture)



#### Jeffrey J. Leow, MBBS, MPH

Department of Urology, Tan Tock Seng Hospital, Singapore; Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; Division of Urology and Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA Interests: Health services research; Urology; Surgery; Genomics; Global health

#### Chien-Chang Liao, PhD

School of Medicine, Taipei Medical University, Taiwan; Department of Anesthesiology, Shuan Ho Hospital, Taipei Medical University, Taiwan Interests: Epidemiology; Complications and mortality after surgery; Diabetes; Stroke



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Department of Pharmacy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China Interests: urologic oncology; cancer endocrine therapy; personalized treatment of prostate cancer



#### James R. Mahalik, PhD

Department of Counseling, Developmental, and Educational Psychology, Boston College, Chestnut Hill, MA, USA Interests: conformity to masculinity norms; social influence variables; gender socialization; health behaviors associated with mental and physical health



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Departments of Pediatrics and Population, Family & Reproductive Health, The Johns Hopkins University, Baltimore, MD, USA Interests: Young men's health; Sexual and reproductive health; Access to care; Expectant fatherhood; Sexual and reproductive health care delivery



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Research Center in Sports Sciences, Health Sciences and Human Development (CIDESD), University of Beira Interior, Covilhã, Portugal Interests: Biomechanics; Performance; Training; Computational fluid dynamics; Aquatics Special Issues and Topics in IMR Press journals Special Issue in Sports Biomechanics for Health and Performance



#### Suks Minhas, PhD

Department of Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK Interests: Andrology; Male infertility; Testicular cancer; Peyronie's disease; Micro dissection TESE; Penilereconstruction; Penile implants; Erectile dysfunction; Testis pain; Sexual dysfunction in men; Penile problems; Treatments for male fertility



#### Du Geon Moon, MD, PhD

Department of Urology, Korea University College of Medicine, Seoul, Republic of Korea Interests: Sexual function in male and female; Pediatric urology; Enuresis and nocturia; Laser in prostate and endoscopic surgery; Regenerative medicine



#### Allen F. Morey, MD

Department of Urology, UT Southwestern Medical Center, Dallas, TX, USA Interests: Hemostatic agents; Tissues glues; Urethral reconstruction; Urologic prosthetics; Urologic trauma



#### Brian J. Morris, ScD, PhD

School of Medical Sciences, The University of Sydney, Sydney, Australia Interests: circumcision; renin-angiotensin system; hypertension genetics; healthy aging; longevity genetics



#### **Richard Naspro, MD**

Head of the Department of Urology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy Interests: Minimally invasive urological surgery (Laparoscopy, Robotics and laser technology); Urological oncology (bladder, kidney and prostate cancer); Surgical management of BPH



#### Zeyad D. Nassar, PhD

Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia Interests: Prostate cancer; Metabolism; Drug design; Angiogenesis



### Chirk Jenn Ng, MD

Department of Primary Care Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia Interests: Men's health behaviour; Digital health; Shared decision making; Implementation science



#### Pantelis Nikolaidis, PhD

School of Health and Caring Sciences, University of West Attica, Athens, Greece Interests: exercise physiology; exercise testing; kinesiology



## MiMi Oh, MD

Department of Urology, Korea University College of Medicine, Seoul, Republic of Korea Interests: Urology; Dysuresia



#### Hiroshi Okada, PhD

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#### Takeshi Otsuki, PhD

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Department of Sports and Health, Hwasung Medi-Science University, Hwaseong, Republic of Korea

Interests: sport in society; health behavior; sports organizations; taekwondo research; research methods

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#### Maria Graça Pereira, MD

Department of Applied Psychology, School of Psychology, University of Minho, Braga, Portugal Interests: Chronic illness; Health promotion; Family health psychology; Integrated care Special Issues and Topics in IMR Press journals Special Issue in Impact of somatic disorders and lifestvle behaviors on men's mental health and wellbeing



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Research Department, Srebrnjak Children's Hospital, Zagreb, Croatia; Medical Faculty, University JJ Strossmayer, Osijek, Croatia Interests: Sports medicine; Occupational health; CPET; Lung function diagnostics; Allergy; Pulmonology



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Faculty of Kinesiology, University of Split, Split, Croatia

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#### Ahmad Shabsigh, MD

Department of Urology, the Ohio State University Wexner Medical Center, Columbus, OH, USA Interests: Urologic oncology; Quality and safety; Sexual medicine



## Giuseppe Simone, PhD

IRCCS "Regina Elena" National Cancer Institute, Rome, Italy
Interests: Uro-oncology; Minimally invasive surgery



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Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, India Interests: Male reproductive biology



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Department of Urology, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany Interests: Andrology; Sexual medicine; Erectile dysfunction; Sexual dysfunction; Male infertility; Peyronie's disease; Male hypogonadism



#### Bogdan Socea, MD

Department of Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania Interests: Public health; Pancreatic cancer; Acute pancreatitis; Abdominal compartment syndrome; FAST, POCUS and pulmonary ultrasound; Digestive tumors; Abdominal wall defects: hernias and incisional hernias



#### Martin Stimpfel, PhD

Department of Human Reproduction, Division of Gynaecology, University Medical Centre Ljubljana, Slajmerjeva 3, Ljubljana, Slovenia Interests: Infertility; Assisted reproductive techniques; In vitro fertilization; Stem cells



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Division of Surgery and Interventional Science, University College London, London, UK Interests: Uro-oncology; Bladder cancer; Prostate cancer; Kidney cancer; Robotic surgery



#### Chang Peng (Colin) Teo, MD

National University of Singapore, Singapore city, Sigapore Interests: Andrology; Prostate cancer; BPH; Kidney stones



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University of Malaya eHealth Unit, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia Interests: Men's health; eHealth; Behaviour change; Epidemiology



#### Taohsin Tung, PhD

Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai, Zhejiang, China Interests: Clinical epidemiology; Biostatistics; Disease screening and medical law



#### Vincent VINH-HUNG, PhD

University Hospital of Martinique, Martinique, France Interests: Colorectal cancer; Prostate cancer; Breast cancer; Oropharyngeal cancer; Lung cancer; Head and neck cancer



#### Richard J. Wassersug, PhD

Department of Cellular & Physiological Sciences, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada Interests: Castration; Emasculation; Prostate cancer; Gender theory; Sexology; Androgen deprivation therapy; Estrogen; Transgenderism



#### Xuezhen Yang, MD, PhD

Executive Vice Chair, Department of Urology, The Second Affiliated Hospital of Bengbu Medical College, China Interests: Basic research of prostate cancer; Minimally invasive diagnosis and treatment of urinary system diseases



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Andrology Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, China Interests: Andrology; Men's health; Sexual function; Infertility Special Issues and Topics in IMR Press journals

Special Issue in The State of the Art of Andrology in China



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College of Life Science and Technology and Center for Human Genome Research, Huazhong University of Science and Technology, Wuhan, Hubei, China

Interests: identification of disease-causing genes and molecular mechanism study of neurological diseases; auto-inflammation diseases; other single-gene disorders



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Exercise Psychophysiology Laboratory, Institute of KEEP Collaborative Innovation, School of Psychology, Shenzhen University, Shenzhen, China Interests: lifestyle behaviors and well-being

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Abstract Fu	III Text PDF(1.94MB)	
	Open Access	34
	Original Research	Downloads
		121
	of leg length asymmetry on leg stiffness	Views
and dynar	nic postural stability in vertical landing	
Kewwan Kim,	Kyoungkyu Jeon, Seunghyun Hyun	
	<i>th</i> <b>2022</b> , 18(5),	
122; https://do	bi.org/10.31083/j.jomh1805122	
(This article b	elongs to the Special Issue Sports Injury &	
Rehabilitation	)	
Abstract Fu	III Text PDF(3.29MB)	
	Open Access	88
	Original Research	Downloads
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•	s during isometric squat exercises	
Zho Cui, Ving	Ving Tang, Myoung Kwon Kim	
-	-Ying Tang, Myoung-Kwon Kim <i>Ith</i> <b>2022</b> , 18(5),	
	bi.org/10.31083/j.jomh1805121	
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training program in Korean male youth soccer	
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112; https://doi.org/10.31083/j.jomh1805112

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110; https://doi.org/10.31083/j.jomh1805110

(This article belongs to the Special Issue Impact of somatic disorders and lifestyle behaviors on men's mental health and wellbeing)

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Review

## Changes in the treatment landscape for metastatic urothelial cancer: current therapy and future directions

Sang Hoon Yeon, Hyo Jin Lee *J. Mens. Health* **2022**, 18(5), 107; https://doi.org/10.31083/j.jomh1805107

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Case Report

Intravesical reservoir erosion as a late complication of a 3-piece inflatable penile prosthesis: ectopic placement in a high-subrectus space: a rare case report

Raidh Talib, Mustafa Alwani, Aksam Yassin, Omar Obeidat,
... Abdulla Al Ansari *J. Mens. Health* 2022, 18(5),
106; https://doi.org/10.31083/j.jomh1805106
(This article belongs to the Special Issue The treatment of LUTS/BPE)

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Original Research

## An update in improving erectile dysfunction therapy in Indonesia by using Li-ESWT and tadalafil combination — vascular endothelial growth factor and peak systolic velocity comparison: a randomized clinical trial

Androniko Setiawan<sup>1</sup>, Andrian Japari<sup>1,\*</sup>, Rosy Nur Febriani<sup>1</sup>, Silvia Werdhy Lestari<sup>2</sup>, Tjahjo Djojo Tanojo<sup>3</sup>, Maria Paulina Budyandini Dyah Pramesti<sup>4</sup>, Agustinus Agustinus<sup>4</sup>, Mu-hammad Hidayat Surya Atmaja<sup>5</sup>, Munawaroh Fitriah<sup>6</sup>, Budi Utomo<sup>7</sup>

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## Abstract

**Background**: Erectile dysfunction (ED) affects men's life desperately and the incidence increases continuously. There are a few lines of ED therapy, but there are still many ED cases that have not treated utterly. Therefore, research is needed to obtain the most appropriate line of ED therapy, based on the underlying mechanism of ED. The aim of this study is to analyze the effect of oral daily 2.5 mg of tadalafil administration and twice weekly Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) for 4 weeks in erectile dysfunction patients, based on Peak Systolic Velocity (PSV) and Vascular Endothelial Growth Factor (VEGF). **Methods**: A 26-sample clinical trial was conducted with pre and post-test control group design. Random allocation was done to divide the samples into two groups. Control group was given 2.5 mg oral daily tadalafil, while the experimental group, additional twice weekly Li-ESWT was given. Therapies were given for 4 weeks. All subjects were assessed using Erection Hardness Score (EHS) score, International Index of Erectile Function (IIEF-5) score, and Color Doppler Ultrasonography (CDUS) penis for PSV, and plasma level of VEGF twice, prior to and after therapy. **Results**: The experimental group showed significant improvement compared to the control group in EHS (delta) 2 (1–2) vs 1 (0–2); IIEF-5 (delta) 7 (3–15) vs 4 (0–11); PSV (delta) 2.60  $\pm$  1.34 vs 1.28  $\pm$  1.86; and VEGF (delta) 26.69  $\pm$  24.23 vs 6.32  $\pm$  25.43. **Conclusions**: Li-ESWT and tadalafil combination therapy improved erectile dysfunction, specifically based on PSV and VEGF parameters.

Keywords: Erectile dysfunction; Li-ESWT; Tadalafil; PSV; VEGF

## 1. Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and maintain penile erection sufficient for satisfactory sexual performance that last for at least three months [1,2]. ED incidence is increasing nowadays, especially in the older population. ED has a great impact in men's life [3]. Generally, ED can be classified into two major groups, which are psychogenic and organic ED [4]. The majority of the cases are organic ED. And, to be specific, the origin of these cases was due to the arterial vasculogenic problem [4]. In arterial vasculogenic ED, the main culprit is thought to be the endothelial dysfunction, which is nowadays commonly caused by metabolic disorders, such as diabetes, hypertension, and metabolic syndrome [2,5–8]. Other causes of organic ED are neurogenic problems, medications side effects, and endocrine disorders.

There are various therapeutic options that can be cho-

sen to improve ED. As the first-line therapies there are Phosphodiesterase type 5 (PDE-5) inhibitors and vacuum devices. While for the second line therapy is intracavernosal injection, and for the third line therapies are penile surgery and prosthesis [9,10]. In Indonesia, the available therapeutic strategy is merely by using oral PDE-5 inhibitors. Other treatment strategies cannot be implemented due to the unavailability of the drug and other modalities. A new modality, Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT), which had been used overseas for erectile dysfunction was brought forward as a new hope for ED treatment in Indonesia [11-23]. Li-ESWT is considered as a restorative therapy which could modify the ability of the penile vasculature in order to achieve a better erection [22,24,25]. The mechanism behind the Li-ESWT was still in debate, but in previous animal studies, it was found that Li-ESWT could induce the increase of Vascular Endothe-

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Characteristics		Control group	Experimental group	Total	n
		n = 12	n = 14	n = 26	p
Mean age (years old)		47.8	49.2	48.6	0.419
Mean spouses' age (years old)		44.7	45.9	45.3	0.620
Mean duration of ED (years)		1.7	3.4	2.6	0.147
Mean of waist circumference (cm)		91.4	97.9	94.9	0.118
Mean BMI (kg/m <sup>2</sup> )		25.7	27.5	26.7	0.277
	Diabetes mellitus	25%	42.9%	34.6%	
	Hypertension	33.3%	42.9%	38.5%	
	Cardiac problems	16.7%	21.4%	19.2%	
Comorbidities	Dyslipidemia	25%	50%	38.5%	
Comorbidities	Hypogonadism	0%	35.7%	19.2%	
	History of smoking	41.7%	28.6%	34.6%	
	History of alcoholism	8.3%	7.1%	7.7%	
	Other	50%	57.1%	53.8%	
	Mild	58.3%	35.7%	46.2%	
ED severities	Mild-Moderate	16.7%	35.7%	26.9%	
	Moderate	25%	28.6%	26.9%	
Median of EHS		2 (1-3)	2 (1-3)	2 (1-3)	0.573
Median of IIEF-5		16.5 (9–21)	15.5 (10-20)	16 (9–21)	0.716

Table 1. Subjects characteristics.

Note: n, number of samples; ED, erectile dysfunction; BMI, body mass index; EHS, Erection Hardness Score; IIEF, International index of erectile function.

Comparison of IIEF-5, EHS, and mean duration of ED were done using Mann-Whitney test, as for other parameters, Independent *t*-test were used.

lial Growth Factor (VEGF), which can lead to angiogenesis [20,21,24,26–32]. Preliminary studies in human also resulting the same result [33]. Angiogenesis or neovascularization could be observed by using Peak Systolic Velocity (PSV) parameter by using Color Doppler Ultrasonography (CDUS). Few studies tried to assess PSV in flaccid state with various results, but it seemed that the result can be a predictive value [34–37].

In order to improve the treatment of erectile dysfunction in Indonesia, especially in Surabaya, East Java, we conducted an experimental study on the combined treatment of Li-ESWT and tadalafil at Soetomo Doctor Hospital in Surabaya. This study is the first study to use Li-ESWT to improve erectile dysfunction by examining VEGF and PSV parameters.

## 2. Materials and methods

## 2.1 Study setting

This randomized controlled, prospective clinical trial aims to evaluate the improvement of patients with erectile dysfunction treated with the combination of Li-ESWT and tadalafil based on VEGF and PSV parameters. The experiment took place in Andrology Clinic, Dr. Soetomo Hospital, Indonesia, between December 2019 and June 2020.

#### 2.2 Subjects

Thirty men with age ranged from 40 to 55 years old, with ED history for at least 3 months, from our center (Andrology Clinic of Dr. Soetomo Hospital) were recruited in this study. The inclusion criteria were patients with mild, mild-moderate, and moderate ED, married and living with their spouses. While the exclusion criteria were psychogenic ED, physical trauma on genital area, spinal cord injury, malignancy, PDE-5 inhibitors contraindications, prior use of PDE-5 inhibitors, and anti-VEGF medication use (one month), and other conditions which render difficulties in implementing the Li-ESWT procedure.

### 2.3 Study protocols

A thorough clinical examination according to the study protocols, which consist of history taking, physical examination, CDUS for PSV and plasma VEGF level examinations were performed by all subjects prior the study. All subjects were given 2.5 mg daily oral tadalafil for 4 weeks as the first line therapy for ED according to the clinical guideline of our clinic. The Li-ESWT procedures were performed twice weekly for 4 weeks along with the 2.5 mg daily oral tadalafil therapy for the subjects in the experimental group. Placebo was not used in this study due to ethical considerations. At the end of therapy, the same examinations were done to all subjects thoroughly in order to get the post experiment results.



 Table 2. Comparison of IIEF-5 scores.

Subject	IIEF-5 score			Pre-test-post-test comparison
Subject	Pre-test	Post-test	Delta	р
Control group (n = 12)	16.5 (9–21)	21 (9–25)	4 (0–12)	0.004*
Experimental group (n = 14)	15.5 (10–20)	23.5 (14–25)	7 (3–15)	0.001*
Total (n = 26)	16 (9–21)	22 (9–25)	5.5 (0–15)	

Note: IIEF, International index of erectile function; n, number of sample; \*, sign of significance (p < 0.05).

Comparison of pre- and post-test IIEF-5 parameter was done using Wilcoxon's test.

#### 2.4 Examination procedure

Erectile dysfunction was evaluated by Erection Hardness Score (EHS) and International Index of Erectile Function (IIEF) scores. EHS scores were obtained directly by asking the subjects after a brief explanation, while IIEF-5 scores were gained from the IIEF questionnaires which were filled by all subjects. Physical examinations were performed by the attending doctors in the Andrology Clinic which were not involved in this study. CDUS for PSV examinations were performed in the Radiology Unit of Dr. Soetomo Hospital by using GE Logiq 9 (GE Healthcare, Chicago, IL, USA). The plasma VEGF levels were measured using Raybiotech® Human VEGF-A ELISA kit (RayBiotech, Peachtree Corners, GA, USA), and the assays were done in the Clinical Pathology Laboratory of Dr. Soetomo Hospital.

### 2.5 Li-ESWT procedure

Li-ESWT procedures were performed by using BTL-6000 SWT Topline machine (BTL Industries, London, UK), with a 15 mm radial probe. Commercially made water-based gel was applied to the penis before Li-ESWT procedures. There were numerous earlier studies regarding the protocols of Li-ESWT for ED. In this study, Li-ESWT was delivered to five locations on the penis, which were distal, medial, and proximal portion of the penile shaft, and to the left and right crux of the penis. Energy density was set at 0.09 mJ/mm<sup>2</sup>, frequency was set at 5 Hz, with a total of 300 shocks at each treatment point.

### 2.6 Tadalafil administration

Tadalafil (Cialis, Eli Lilly, UK) was administered 2.5 mg oral daily.

## 2.7 Statistical analysis

The statistical analysis was done by using Easy R (EZR) statistical software version 1.54 (Jichi Medical University, Saitama Medical Center, Saitama, Japan) [38]. The data are expressed in mean  $\pm$  SD or median and range. Comparisons were done using paired *t* test or Wilcoxon

signed-rank test as appropriate for the between group preand post-test comparisons. As for the comparison between the experiment group and the control group, the independent *t* test or Mann-Whitney test is used as appropriate. Significance was set at 5% (p < 0.05).

## 3. Results

The baseline assessment prior to the study that shown in Table 1 were similar. There was no significant difference between the control and the experimental group (p >0.05). Before starting the study, both groups showed similar baseline conditions. Three men in the control group and one man in the experimental group withdrew from the study due to personal problems.

At the end of the treatment, there were changes in IIEF-5 questionnaire scores and EHS scores in both groups. In Tables 2,3, the IIEF-5 questionnaire score in the control group increased 4.5 points (p = 0.004) and 1 point for EHS score (p = 0.004), while in the experimental group, the score increased 8 points for IIEF-5 questionnaire score (p = 0.001) and 2 points increase for the EHS score, (p = 0.001). In Table 4, there were no significant changes of VEGF level in control group although VEGF level increased 6.32 points (p = 0.408); however there were significant changes of the VEGF level in the experimental group with 26.7 points increase (p = 0.001). In Table 5, the PSV parameters of the two groups have significant changes, and the control group increased by 1.28 points (p = 0.004) and 2.60 points increase in experimental group (p = 0.001).

In Table 6, we compared the changes in the control with the experimental group to determine the efficacy of the therapy. Although the post-test result didn't seem to differ significantly, but after calculating the changes of the respective parameters (delta), we can see that between two groups there are significant statistical differences. The changes of IIEF-5 questionnaire score and EHS score in the experimental group showed more superior result than control group (p = 0.047 and p = 0.032 respectively). Experimental group had a better improvement in penile vascularization which was shown from the PSV parameter signifi-

EHS core Pre-test-post-test comparison Subject Pre-test Post-test Delta р Control group 0.004\* 2 (1-3) 3 (1-4) 1(0-2)(n = 12)Experimental group 2 (1-3) 0.001\* 4(3-4)2(1-2)(n = 14)Total 2(1-3)3.5 (1-4) 1(0-2)

Table 3. Comparison of EHS scores.

Note: EHS, Erection Hardness Score; n, number of sample; \*, sign of significance (p < 0.05). Comparison of pre- and post-test EHS parameter was done using Wilcoxon's test.

Table 4. Comparison of VEC	<b>JF</b> values.
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Subject	VEGF level (pg/mL)			Pre-test-post-test comparison	
Bubjeet	Pre-test	Post-test	Delta	р	
Control group (n = 12)	$59.92 \pm 41.91$	$66.24 \pm 49.42$	$6.32\pm25.43$	0.408	
Experimental group (n = 14)	$57.95 \pm 25.92$	$84.65\pm40.71$	$26.69\pm24.23$	0.001*	
Total (n = 26)	$58.86\pm33.52$	$76.15\pm44.99$	$17.29\pm26.40$		

Note: VEGF, Vascular Endothelial Growth Factor; n, number of sample; \*, sign of significance (p < p0.05).

Comparison of pre- and post-test VEGF parameter was done using paired t-test.

Table 5. Comparison of PSV values.					
Subject	PSV (cm/s)			Pre-test-post-test comparison	
	Pre-test	Post-test	Delta	р	
Control group $(n = 12)$	$11.40\pm3.47$	$12.68\pm3.90$	$1.28 \pm 1.86$	0.04*	
Experimental group (n = 14)	$11.14 \pm 1.79$	$13.74\pm2.10$	$2.60 \pm 1.34$	0.001*	
Total $(n = 26)$	$11.26 \pm 2.64$	$13.25\pm3.04$	$1.99 \pm 1.70$		

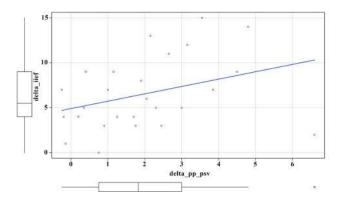
## Companison of DSV values

Note: PSV, Peak Systolic Velocity; n, number of sample; \*, sign of significance (p < 0.05).

Comparison of pre- and post-test PSV parameter was done using paired t-test.

cant changes compared to control group (p = 0.009). The VEGF level also showed better improvement in experimental group compared to control group, and it was statistically significant (p = 0.023). The increase of all parameter in the experimental group are higher than in the control group, which mean that the addition of Li-ESWT to the standard therapy provided more outstanding result.

(n = 26)



Furthermore, Fig. 1 showed a positive correlation (by using Spearman correlation test) between changes in the IIEF-5 questionnaire score and changes in the PSV parameter significantly (p = 0.048).

Fig. 1. Correlation of delta PSV and IIEF-5.

Table 6. Comparison of all parameters between groups.

Parameter		Control group	Experimental group	р
	Pre-test	16.5 (9–21)	15.5 (10-20)	0.716
IIEF-5	Post-test	21 (9–25)	23.5 (14–25)	0.047*
	Delta	4 (0–11)	7 (3–15)	0.047*
	Pre-test	2 (1-3)	2 (1-3)	0.573
EHS	Post-test	3 (1-4)	4 (3–4)	0.018*
	Delta	1 (0–2)	2 (1–2)	0.032*
	Pre-test	$59.92 \pm 41.91$	$57.95 \pm 25.92$	0.885
VEGF	Post-test	$66.24\pm49.42$	$84.65\pm40.71$	0.308
	Delta	$6.32\pm25.43$	$26.69\pm24.23$	0.023*
	Pre-test	$11.40\pm3.47$	$11.14\pm1.79$	0.813
PSV	Post-test	$12.68\pm3.90$	$13.74\pm2.10$	0.385
	Delta	$1.28 \pm 1.86$	$2.60\pm1.34$	0.009*

Note: IIEF, International index of erectile function; EHS, Erection Hardness Score; PSV, Peak Systolic Velocity; VEGF, Vascular Endothelial Growth Factor; \*, statistically significant (p < 0.05). Comparison between groups for pre-test and post-test VEGF parameters were done using Independent *t*-test, as for the others parameters, the statistics methods used was Mann-Whitney test.

## 4. Discussion

The prevalence of erectile dysfunction remains high up until now, especially the organic ED that caused by arterial vasculogenic problems, and the PDE-5 inhibitors are still the main choice of therapy for this kind of ED [1,39]. But, the underlying cause behind the occurrence of arterial vasculogenic ED, which is believed to be the endothelial dysfunction, is still remain untouched. The therapy should be focused toward the endothelial dysfunction, which up until now, is still not solved by PDE-5 inhibitors as the first line therapeutic option. Newer therapies have been invented to improve ED, but almost none of them are focused on repairing the endothelial function. Regenerative therapies, such as stem cells, theoretically are able to repair these underlying mechanisms, but still no astonishing result was seen. Shock wave, especially low intensity shock wave, which is delivered from extra corporeal, seems to have a capability to induce regenerative process to repair the endothelial function. Prior studies have shown promising results.

In this study, we want to dwell further into Li-ESWT effects, clinically, as well as biochemically and radiologically, by assessing changes on IIEF-5 questionnaire score and EHS score, and evaluating the vascular regeneration process of the penile based on PSV parameter, and VEGF level as an angiogenesis factor.

In ED, CDUS is used to monitor the blood flow in cavernous arteries to confirm the penile vasculature [35,40– 43]. CDUS could be done in two conditions, flaccid state and full erect state, with CDUS in fully erect state being the gold standard. The procedure requires the use of intracavernous injection of vasoactive agents to stimulate the erect state (Pharmacopenile Doppler Ultrasonography) [19,44– 47]. On the contrary, CDUS in flaccid state is done without any stimulation to the penis. Assessment in flaccid state is considered more comfortable than Pharmacopenile Doppler Ultrasonography (PPDU), because it is a non-invasive assessment. CDUS of the flaccid penis, according to studies could equally reflect penile vasculature condition as the fully erect state [34–37,48]. Parameter to be assessed in CDUS are arterial diameter, Peak Systolic Velocity (PSV), and Resistive Index (RI). But, in flaccid state, only PSV which had a significance in determining ED and for monitoring therapy.

In addition, VEGF is a protein belonging to the growth factor family and has a unique role in stimulating vascular regeneration [22,49,50]. There are five isoforms of VEGF have been known up until now, which are VEGF-A, VEGF-B, VEGF-C, VEGF-D, and Placenta Growth Factor (PGF) [51]. The receptors of VEGF-A are found on the endothelial tissue. VEGF-A is known for having the effect to stimulate the blood vessel angiogenesis process due to hypoxic condition and tissue trauma [52]. There was no previous study about VEGF parameter for evaluation of Li-ESWT therapy.

The mechanism behind ESWT is micro trauma. Low intensity shock waves which were delivered to the cavernous tissues causing micro traumas in the cavernous tissues. In regard most cavernous tissue are consisted of vasculature tissue (sinuses and vessels), the micro traumas were expected to happen in the vasculature tissues. The traumas, specifically being shear trauma, induce the release pro-inflammatory substances which lead to the release of the pro-angiogenesis substances, such as VEGF.

In the control group, there was clinical improvement and increased PSV parameters without any significant changes in VEGF levels. As stated before, PDE-5 inhibitor do indeed improve the clinical outcome of ED. That is the main cause of its being the chosen therapy for first line treatment. The increase of PSV in the control group might be caused by the vasodilatation in the penile vasculature as the main effect of the inhibition of PDE-5 enzyme. The unchanged level of VEGF showed that PDE-5 inhibitor does not have the capability to repair the endothelial dysfunction which was the underlying mechanism of this type of ED.

Meanwhile, in the experimental group, the increase in PSV and VEGF levels supported the clinical improvement, which was higher than that in the control group. The tremendous increase of PSV and VEGF in the experimental group was likely due to the Li-ESWT procedure (in regard that the PDE-5 inhibitor effect is same). Li-ESWT induced micro trauma caused by the shear process done in the tissue from the shock wave movement in the penile perivascular tissue, which then stimulating the regeneration process by attracting the pro-inflammatory substances, and pro-proliferative substances, such as VEGF, which then stimulated the generation of new blood vessel in the cavernous tissue. These results have shown that tadalafil alone could not achieve significant increase in VEGF level (in control group), while the addition of Li-ESWT procedure to the tadalafil therapy produced better results. Li-ESWT was proven to be more superior to tadalafil therapy in this case, or maybe this effect happened due to the synergism of both tadalafil and Li-ESWT therapies. Nevertheless, it is clear that PDE-5 inhibitor only focused on vasodilatory effect, whilst Li-ESWT had done more by repairing the underlying mechanism. But, of course, the effect of Li-ESWT is not instantaneous, that is why Li-ESWT is better if used as a combination with other means of therapy [53].

Previous studies have similar results in terms of clinical improvement and sexual satisfaction [13,14,54–56]. Meanwhile, a previous study used PSV parameters in a relaxed state to evaluate the efficacy of Li-ESWT, and the results were similar to our study [48]. As for the assessment of VEGF levels, no human studies have been published before. This study was the first study to improve the erectile dysfunction that using Li-ESWT by examining the VEGF and PSV parameters.

## 5. Conclusions

This trial proved that the combination therapy of 2.5 mg oral daily tadalafil and twice weekly Li-ESWT were superior to 2.5 mg oral daily tadalafil alone in improving IIEF-5 score, EHS score, PSV parameters, and plasma level VEGF in mild, mild-moderate, and moderate erectile dysfunction patients. In conclusion, the combination therapy of Li-ESWT and tadalafil improved erectile dysfunction, specifically based on PSV and VEGF parameters.

## Author contributions

AS, AJ, RNF, and TDT designed the research study. AJ, AS, and RNF performed the research. MF provided help and advice on clinical laboratory results. MHSA provided help and advice on radiological results. BU provided help and advice on statistical method. AJ, AS, RNF, AA, MPBDP, TDT analyzed the data. AS, AJ, SWL wrote the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was approved by Ethical Board for Health Research, Universitas Airlangga and Dr. Soetomo Hospital with ethical certificate number 1690/KEPK/XII/2019. Written informed consents were obtained from all participants prior to the study. This study was also registered in ClinicalTrials.gov with Registration ID: NCT05043896.

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## **Conflict of interest**

The authors declare no conflict of interest.

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