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Review Article

Potential Applications of Low-intensity Extracorporeal Shock-Wave Therapy in Urological Diseases via Activation of Tissue Resident Stem Cells

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Abstract

For many years, low-intensity extracorporeal shock-wave therapy (Li-ESWT) has been clinically applied as a noninvasive therapeutic method, for urological diseases. The major corresponding biological molecular mechanisms of Li-ESWT are to induce stem cell differentiation, neural regeneration, and angiogenesis. This narrative review aims to present an overview of the potential utility of Li-ESWT and its effects on stem cell therapies. Recent studies have also shown that the combination treatment of Li-ESWT and stem cell therapies can be a new option for the treatment of erectile dysfunction (ED), urinary incontinence, bladder dysfunction, and other diseases. The potential contributions of Li-ESWT on stem cell therapies for these diseases are studied, highlighting the influence of Li-ESWT on proliferation, viability, and differentiation capacity of certain stem cells. The potential mechanisms, including the increased expression of vascular endothelial growth factor, chemokine CXC motif ligand 5, and transforming growth factor-β1 are described herein. Li-ESWT can also activate many cellular signaling pathways. The combination of Li-ESWT and stem cell therapies is a promising strategy for urological diseases. However, a much greater understanding of the mechanisms by which Li-ESWT enhances the efficacy of stem cell therapy is still needed before this combined treatment can be recommended for large-scale clinical application.

Keywords: Activation, bladder dysfunction, erectile dysfunction, low-intensity extracorporeal shock wave therapy, mechanism, stem/progenitor cells, urinary incontinence

Introduction

Low-intensity extracorporeal shock-wave therapy (Li-ESWT) is a form of energy transfer that is <0.2 mJ/mm^2 than the ESWT employed for lithotripsy and nephrolithiasis treatment. This lower intensity, with the appropriate dosage of energy transfer, is thought to induce beneficial effects in human tissues. Li-ESWT has been used to treat ischemic heart disease,[1] musculoskeletal disorders,[2] erectile

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dysfunction (ED),[3] and urinary incontinence (UI)[4] for many years. The mechanisms underlying Li-ESWT include tissue regeneration,[5] angiogenesis,[6] reduction of inflammation,[7] and stem cell activation and recruitment.[8]

Stem cell therapies have also been studied for several years with the goal of replacing lost or damaged cells.[9] In recent years, different approaches for stem cell acquisition included procurement from multiple sources and for delivery included seeding of stem cell lysate and stem cells on tissue.[10] However, the limitations of exogenous stem cells in therapeutic applications have become obvious. It has been reported that migration of implanted stem cells enhanced tumor growth.[11] Therefore, activation of endogenous stem cells by Li-ESWT offers an ideal therapy and avoids the potential complications of traditional stem cell therapies. In this review, we summarize the interactions between Li-ESWT and stem cell therapies.

Low-intensity Extracorporeal Shock-Wave Therapy and Erectile Dysfunction

Over the past decade, Li-ESWT has evolved from an experimental therapy to an exciting potential treatment option for ED. The use of Li-ESWT in the treatment of ED was first reported in 2010,[12] in a study which assessed the efficacy of Li-ESWT in patients with ED with a 6-month follow-up. Since then, an increasing amount of evidence has suggested that Li-ESWT is an effective approach for ED. Specifically, clinical research showed improvement in IIEF-EF score and a high rate of conversion of nonresponders to phosphodiesterase type-5 inhibitors after the application of Li-ESWT.[13,14] Animal studies have also revealed that Li-ESWT could promote the regeneration of endothelial cells and smooth muscle, which ultimately improves erectile function.[5,15] In addition, studies have demonstrated that Li-ESWT could partially ameliorate diabetes mellitus-associated ED by promoting the regeneration of neuronal nitric oxide synthase (nNOS)-positive nerves, endothelium, and smooth muscle in the penis. These beneficial effects appear to be mediated by the recruitment of endogenous mesenchymal stem cells (MSCs).[5] Recently, combination therapies of stem cells with drugs, herbs, and Li-ESWT have shown better results compared with single treatment. The combination of Li-ESWT with stem cells has attracted much attention because Li-ESWT is a noninvasive technique with a major advantage of possible restoration of natural penile erections. Moreover, Li-ESWT is an ED treatment with the potential for an actual cure.[16]

Lin *et al*.[8] confirmed that Li-ESWT increased EdU + cells within the subtunical spaces in penile erectile tissue. Li-ESWT also stimulated cell proliferation of endothelial and Schwann cells through the Erk1/2 pathway. In another study,[17] Li-ESWT was shown to restore penile smooth muscle and endothelium content and to reduce lipid accumulation. Collectively, these studies suggest that the mechanism underlying Li-ESWT appears to be the activation of stem/progenitor cells *in situ*, which prompts cellular proliferation and accelerates penile tissue regeneration.

Interestingly, Li-ESWT was also shown to improve the survival of transplanted stem cells. Shan *et al*. indicated that the combination of Li-ESWT with bone marrow MSCs (BMSCs) transplantation improved erectile function in diabetic rats more effectively than Li-ESWT or BMSC transplantation performed alone.[18] It is postulated that Li-ESWT increases the expression of stromal cell-derived factor-1 (SDF-1), which inhibits the migration of BMSCs and facilitates the retention of BMSCs in the cavernous body. Moreover, Li-ESWT enhanced revascularization in the cavernous body, which may create a supportive environment in which the transplanted BMSCs thrive. The application of adipose-derived stem cells (ADSCs) along with Li-ESWT could improve ED by enhancing the expression of alpha-smooth muscle actin (α-SMA), nNOS, and Von Willebrand factor in the corpus cavernosum of rats with ED. In a rat model of post-prostatectomy ED, the combination of ADSCs and Li-ESWT showed enhanced recovery of erectile function.[19] The results demonstrated that ADSCs enhance nerve regeneration by increasing β-III tubulin and nNOS expression. In addition, Li-ESWT is capable of significantly upregulating the expression of vascular endothelial growth factor (VEGF) and inducing neovascularization on the cavernous nerve as well as improving vascular supply to the penis and decreasing apoptosis of cells in the corpus cavernosum. Furthermore, combination therapy with Li-ESWT and MSCs was confirmed to be more effective for ED than either treatment alone.[20] In summary, previous studies proved that the combination of Li-ESWT and stem cells had a greater impact on ED than stem cells therapy or Li-ESWT treatment alone; however, the interactions between stem cells and Li-ESWT, as well as the potential side effects of combination therapies, remain poorly defined. According to early studies, Li-ESWT contributes to the proliferation, differentiation, and paracrine effects of stem cells.[21,22] Jeon *et al*. also investigated the mechanism of combined Li-ESWT and MSCs therapy in a rat model of diabetic ED.[23] They found that the quantity of MSCs could be significantly increased by Li-ESWT treatment. Furthermore, Li-ESWT could induce MSCs to express more VEGF *in vivo* and *in vitro,* which contributed to autophagy by triggering the PI3K/AKT/mTOR and NO/cGMP signaling pathways. In addition, Li-ESWT could be an effective tool for accelerating the production of and increasing the concentration of VEGF during the application of stem cell therapy.[24] It has been demonstrated that Li-ESWT could promote angiogenesis and proliferation by activating penile progenitor cells in the diabetes mellitus-associated ED (DMED) microenvironment, which was consistent with the results obtained in animals.[23] Li-ESWT promoted the expression of SDF-1 and platelet endothelial cell adhesion molecule-1 in DMED rats, which can attract stem cells to the corpus cavernosum.

Low-intensity Extracorporeal Shock-Wave Therapy and Urinary Incontinence

Both clinical and preclinical studies have demonstrated that Li-ESWT is a potential noninvasive therapy for UI owing

to its capability to stimulate striated muscle growth and tissue regeneration.[4,25,26] The striated urethral sphincter plays a crucial role in continence for both men and women. Striated muscle, also known as skeletal muscle, is composed of multinucleated contractile muscle cells called myofibers. During development, myofibers are formed by fusion of mesoderm progenitors called myoblasts, which originate from satellite cells. Satellite cells, also known as muscle stem cells, play an essential role in muscle regeneration and functional recovery by virtue of their intrinsic ability to generate a large number of new myofibers.[27] One important finding demonstrated that Li-ESWT induces muscle regeneration by stimulating satellite cell myogenic differentiation.[28] Thus, Li-ESWT could increase the number of progenitor cells in the urethra and enhance the recruitment of MSC with increased expression of VEGF.[4,26,29]

Low-intensity Extracorporeal Shock-Wave Therapy and Bladder Dysfunction

Recent research demonstrated that stem cell therapy for bladder dysfunction (BD) could be enhanced by Li-ESWT.[30] BD is considered a suitable urologic disease for stem cell therapy because its underlying pathophysiology involves neuropathy and vasculopathy. However, previous study found that 40%–60% of samples from a BD rat model showed no response to ADSCs treatment.[31] Nevertheless, the therapeutic effect of ADSCs injection could be improved by Li-ESWT.[32] Notably, only 52.3% of BD rats had normal voiding function after ADSCs injection, whereas up to 75.0% showed a normal voiding pattern after combined application of Li-ESWT with ADSCs. These results demonstrate that Li-ESWT-treated ADSCs had the best efficacy in treating diabetic BD due to secretion of VEGF and nerve growth factor (NGF), which enhance vascular and neural regeneration.

The same authors also verified Li-ESWT to be a promising trigger for the secretion of cytokine and growth factors, such as NGF and VEGF, by ADSCs. This study improved innervation and vascularization of the bladder *in vivo*.[33] The improvement of diabetic BD may be due to the recruitment of endogenous stem cells to the bladder by Li-ESWT.

Low-intensity Extracorporeal Shock-Wave Therapy and Other Diseases

Li-ESWT has been considered a noninvasive, effective, versatile, and repeatable therapy for the treatment of several musculoskeletal diseases and for some pathological conditions in which regenerative effects are desirable, particularly if other noninvasive or conservative therapies have failed.[34] Moreover, experimental and clinical studies demonstrate that the efficacy of ESWT in accelerating tissue repair and regeneration in various wounds.[34-36] In a tissue ischemia model,[6] Li-ESWT mobilized endothelial progenitor cells to the target organ to facilitate angiogenesis.

Li-ESWT has been known to promote tissue regeneration after sports injuries and enhances blood flow in muscle tissue shortly after the application.[37] The biological responses triggered by Li-ESWT include the recruitment of MSCs, stimulation of cell proliferation and differentiation, and anti-inflammatory effects. These are considered important therapeutic effects of Li-ESWT for soft-tissue wound healing.[38]

Li-ESWT has been reported to enhance the proliferation and function of BMSCs. The Li-ESWT activated BMSCs secrete more VEGF and chemokine CXC motif ligand 5 than untreated BMSCs. The treated BMSCs also demonstrated a higher capacity to promote angiogenesis and nerve regeneration *in vitro* in a high-glucose medium. The authors suggested that the transplantation of Li-ESWT-treated BMSCs might promote tissue regeneration in diabetes.[21] In a rat model of chronic hind limb ischemia, combined Li-ESWT and endothelial progenitor cells (EPCs) treatment significantly improved blood flow recovery. The improved efficacy is believed to be a result of increased tissue expression of chemoattractant factors such as SDF-1 and VEGF. These factors are crucial for the recruitment of circulating EPCs during acute ischemia.[39]

In vitro research has also demonstrated that Li-ESWT facilitates the proliferation and differentiation of neural stem cells, which play a pivotal role in the repair of brain function in the diseases of the central nervous system.[40] Furthermore, Li-ESWT reduces the risk of skin and tissue fibrosis. Rinella *et al*. studied the effects of Li-ESWT in modulating the differentiation of human ADSCs toward myofibroblasts. The results show that Li-ESWT downregulated the expression of the myofibroblast marker α-SMA and the extracellular matrix protein type I collagen. Moreover, Li-ESWT reduced the expression of integrin alpha 11, a major collagen receptor in fibroblastic cells that is involved in the differentiation of myofibroblast.[41]

Li-ESWT is also a useful noninvasive therapy for human bone fracture repair.[42-44] In bone, Li-ESWT promotes the expression of bone morphogenetic proteins (BMP), collagen type I, and alkaline phosphatase, which play an important role in bone development and fracture healing. Early research reported that Li-ESWT induced satisfactory healing effects of segmental bone defects through the stimulation of MSC recruitment and differentiation into bone-forming cells by increasing the expression of transforming growth factor (TGF)-β1 and VEGF-A mRNA.[45] Another clinical study reported that systemic concentrations of NO, TGF-β1, VEGF, and BMP-2 increased dramatically after 1 month of ESWT in patients with long bone nonunions.[46] The satisfactory results verified the positive therapeutic effect of ESWT for bone fractures. In addition, ESWT had positive effects on osteoblast proliferation by upregulating the expression of genes that participate in skeletal development and osteoblastic lineage differentiation.[47]

Cellular Signaling Pathways Involved in Li-ESWT-Induced Stem Cell Activation

Li-ESWT regulates cellular signaling pathways, thereby affecting the transcription and modification of intracellular proteins. Specific cellular processes/molecules modulated by Li-ESWT include protein kinase RNA-like endoplasmic reticulum kinase/activated transcription factor (PERK/ATF), Wnt/β-catenin, and extracellular-signal-regulated kinase (ERK).

Protein Kinase RNA-Like Endoplasmic Reticulum Kinase/Activated Transcription Factor Signaling Pathway

PERK is an important pathway responsible for the attenuation of the overloaded misfolded proteins, consequently attenuating endoplasmic reticulum stress. PERK phosphorylation activates the α subunit of eukaryotic initiation factor 2, which subsequently allows the translation of UPR-dependent genes, such as ATF4.[48]

Recently, studies have also shown that Li-ESWT activates the PERK/ATF4 pathway to stimulate myotube formation in cultured myoblasts[28] and to increase the expression of brain-derived neurotrophic factor in cultured Schwann cells.[49] These studies elucidate some of the mechanobiological pathways responsible for the clinical improvements observed after Li-ESWT.

Wnt/β-Catenin Cellular Signaling Pathway

The Wnt signaling pathway, a highly conserved sequence across taxa, is a complex network of protein action relevant for embryonic development, neoplasia, and normal physiological processes of adult animals.[50]

The Wnt/β-catenin and Notch pathway also appear to play important roles in the long-term efficacy of Li-ESWT.[40] In one study, Li-ESWT induced penile stem/progenitor cell differentiation into smooth muscle cells through the Wnt/β-catenin signaling pathway in a time- and dosage-dependent manner.[51]

ERK Pathway

Mitogen-activated protein kinases (MAPKs) form major cell-proliferation signaling pathways from the cell surface to the nucleus. There are three major subfamilies of MAPK: ERK, c-Jun N-terminal or stress-activated protein kinases, and MAPK14. MAPK signaling pathways are known to play a central role in the proliferation, differentiation, apoptosis, inflammation, and development of cells. The ERK MAPK is one of the most important pathway for cell proliferation.[52]

Li-ESWT triggers the release of cellular ATP, which subsequently activates purinergic receptors and finally enhances proliferation *in vitro* and *in vivo* through downstream ERK ½ signaling.[53]

Perspectives

Combined therapy between Li-ESWT and stem cells may have added beneficial effects in urological diseases, such as ED, UI, and BD. Studies show that Li-ESWT alone can activate local endogenous stem cells as well as promote the proliferation, differentiation, and migration of stem cells. The combination of BMSCs and Li-ESWT shows significant potential in rehabilitative and orthopedics medicine (tendon pathologies, bone healing, and ischemic bone diseases), dermatology (ulcers, wound healing disturbances, and painful scars), neurology (spastic hypertonia and related syndromes), and ischemic heart diseases. Li-ESWT alone has been considered an effective, safe, versatile, repeatable, and noninvasive therapy. The combination of Li-ESWT and stem cells is a promising therapy in the field of regenerative medicine and tissue engineering. However, the mechanisms involved are not yet fully understood and additional research is warranted from basic science research to large-scale clinical applications before the application of combination therapy.

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Conflicts of interest

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