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# In Situ Activation of Penile Progenitor Cells With Low-Intensity Extracorporeal Shockwave Therapy.

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## Abstract

**BACKGROUND:** We previously reported that progenitor cells, or stem cells, exist within penile tissue. We hypothesized that acoustic wave stimulation by low-intensity extracorporeal shockwave therapy (Li-ESWT) would activate local stem or progenitor cells within the penis, producing regenerative effects.

**AIMS:** To study the feasibility of in situ penile progenitor cell activation by Li-ESWT.

**METHODS:** We performed a cohort analysis of young and middle-age male Sprague-Dawley rats treated with 5-ethynyl-2'-deoxyuridine (EdU) pulse followed by Li-ESWT. In addition, Li-ESWT was applied to cultured Schwann cells and endothelial cells to study the molecular mechanism involved in cell proliferation. Thirty minutes before Li-ESWT, each rat received an intraperitoneal injection of EdU. Li-ESWT was applied to the penis at very low (0.02 $mJ/mm^2$ at 3 Hz for 300 pulses) or low (0.057 $mJ/mm^2$ at 3 Hz for 500 pulses) energy levels. The endothelial and Schwann cells were treated with very low energy (0.02 $mJ/mm^2$ at 3 Hz for 300 pulses) in vitro.

**OUTCOMES:** At 48 hours or 1 week after Li-ESWT, penile tissues were harvested for histologic study to assess $EdU^+$ and $Ki\text{-}67^+$ cells, and cell proliferation, Ki-67 expression, Erk1/2 phosphorylation, translocation, and angiogenesis were examined in cultured Schwann and endothelial cells after Li-ESWT.

**RESULTS:** Li-ESWT significantly increased $EdU^+$ cells within penile erectile tissues ($P < .01$) at 48 hours and 1 week. There were more cells activated in young animals than in middle-age animals, and the effect depended on dosage. Most activated cells were localized within subtunical spaces. In vitro studies indicated that Li-ESWT stimulated cell proliferation through increased phosphorylation of Erk1/2.

**CLINICAL TRANSLATION:** The present results provide a possible explanation for the clinical benefits seen with Li-ESWT.

**STRENGTHS AND LIMITATIONS:** The main limitation of the present project was the short period of study and the animal model used. Li-ESWT could be less effective in improving erectile function in

old animals because of the decreased number and quality of penile stem or progenitor cells associated with aging.

**CONCLUSION:** Li-ESWT activation of local penile progenitor cells might be one of the mechanisms that contribute to the beneficial effects of shockwave treatment for erectile dysfunction, which represents a non-invasive alternative to exogenous stem cell therapy. Lin G, Reed-Maldonado AB, Wang B, et al. In Situ Activation of Penile Progenitor Cells With Low-Intensity Extracorporeal Shockwave Therapy. J Sex Med 2017;14:493-501.



**KEYWORDS:** Endogenous Stem Cells; Erectile Dysfunction; Low-Intensity Extracorporeal Shockwave Therapy; Penile Progenitor Cells; Stem Cells

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