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Low-intensity extracorporeal shock wave therapy in the postoperative management of Fournier`s gangrene - a case series of a new concept

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ABSTRACT

Objectives: Fournier's gangrene is an aggressive frequently fatal polymicrobial soft tissue infection of perineum and external genitalia requiring immediate radical surgery. Postoperative management includes mesh-graft and skin-flaps. We used low intensity shock wave therapy (Li-ESWT) in the management of wound healing following Fournier`s gangrene in three case series.

Materials and Methods: Li-ESWT was applied three times weekly with 2000-3000 shock waves at 3-4 Hz (Energy flux density: 0.25 mJ/mm^2) using Duolith SD1 ultra without anesthesia. In one year, we treated 8 patients at two centers in Europe and Asia. Based on planimetric assessment of the wound area at respective times, we calculated the re-epithelization speed (cm^2/d).

Results: Case series 1: Three patients after secondary healing of a skin flap. In all cases wound-healing was promoted within 6-7 weeks (re-epithelization speed 0.24-0.42 cm^2/d). Case series 2: Two patients were primarily treated successfully over 6-7 weeks with significant closure of the wound (re-epithelization speed 0.65-0.79 cm^2/d) followed by mesh-graft. Case series 3: Three patients exclusively treated by Li-ESWT showed complete restoration of penile and scrotal tissue within 4-5 months (i.e. re-epithelization speed of 0.47-0.70 cm^2/d).

Conclusions: Li-ESWT could become an interesting non-invasive treatment modality for patients with secondary wound problems (i.e. Fournier`s gangrene).

Keywords: Extracorporeal shock wave therapy, Fournier`s gangrene, wound healing, low-intensity ESWT, stem cell proliferation, re-epithelization, planimetric assessment

Introduction

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia (Fig. 1a). It is an anatomical sub-category of necrotizing fasciitis with which it shares a common etiology and management pathway.[1,2] Typically, there is painful swelling of the scrotum or perineum with sepsis. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease.[3]

Risk factors include diabetes mellitus, malnutrition, immunotherapy, alcohol abuse, recent urethral or perineal surgery, and high body mass index.[1-3] The degree of internal necrosis is usually vastly greater than suggested by external signs. It requires immediate radical surgery with complete removal of affected tissue (Fig. 1b).

Once the patient is stabilized and the wounds are clean, postoperative management usually includes mesh-graft and skin-flaps.[3,4] Both can be associated with secondary wound healing problems mostly requiring secondary surgical procedure (Fig. 2a). Moreover, the cosmetic results of mesh-grafts are not convincing, because it is not replacing the previous skin; in case of large excision of scrotal skin, the wound can only be covered by cutaneous flaps.[4] Other alternatives of postoperative wound management have been tested, such as hyperbaric oxygen therapy, application of honey, and vacuum-techniques.[3,5-7] However, a recent meta-analysis did not prove any benefit on wound-healing compared to classical wound dressing.[7]

Among the strategies for chronic wound treatment, extracorporeal shock wave therapy (ESWT) has shown promise. Initially used for treating renal and ureteral calculi as extracorporeal shock wave lithotripsy (ESWL),[8,9] ESWT's success in urology prompted exploration in other areas, including wound healing.[10-13] Unlike to the use of shock waves for stone fragmentation (ESWL, for treatment of soft-tissue usually only low energy flux density is required. Thus, low-intensity shock wave therapy (Li-ESWT) is defined a less than 35 mJ/mm^2 per impulse.[14]

The primary mechanism of action of Li-ESWT is based on the so-called mechano-transduction in the respective cell thereby improving tissue circulation by stimulating the production of energy-rich nitric oxide (NO), leading to reduced muscle rigidity and improved biomechanical functioning, enhancing mobility and self-perception.[15-18] ESWT can also activate key factors involved in connective tissue repair, such as fibroblasts which may increase proliferation and expression of essential factors like TGF-beta-1 and collagen types I and III.[19-21]

Based on these promising results we started to use Li-ESWT in the postoperative management of Fournier`s gangrene. We reported already early case studies.[22,23] In this article, we want to present our mid-term experience at two centers in Europe and Asia with a more extensive evaluation of the wound-healing process focusing on the possible impact of stem cell stimulation.

Material and Methods

PATIENTS:
This is a two-institutional pilot study of case series (SLK Kliniken Heilbronn, Germany, East Avenue Medical Center, Manila, Phillipines): From November 2021 to November 2022, eight men (age 27-68 years) were admitted with severe Fournier`s gangrene requiring complete excision of the scrotal and perineal skin (Fig. 1-4). They were all treated in the Intensive Care Unit (ICU) for 10-14 days (Table 1). Wound dressing was applied every other day.

TREATMENT GROUPS:
The data of all patients are summarized on Table 1.

Case Series 1: Once granulation of the wound started, we usually closed the wound by use of skin flap from the surrounding area. This was performed in the first three patients. Unfortunately, all three showed dehiscence of the wound in the follow-up (Fig. 1). Instead of a secondary surgical procedure we treated the patients by Li-ESWT.

Case Series 2: The next two patients (Group 2) were treated primarily with Li-ESWT without performing early plastic surgery (Fig. 2). Here we planned to perform a delayed surgical closure either by a skin-flap or a mesh-graft.

Fig. 1a

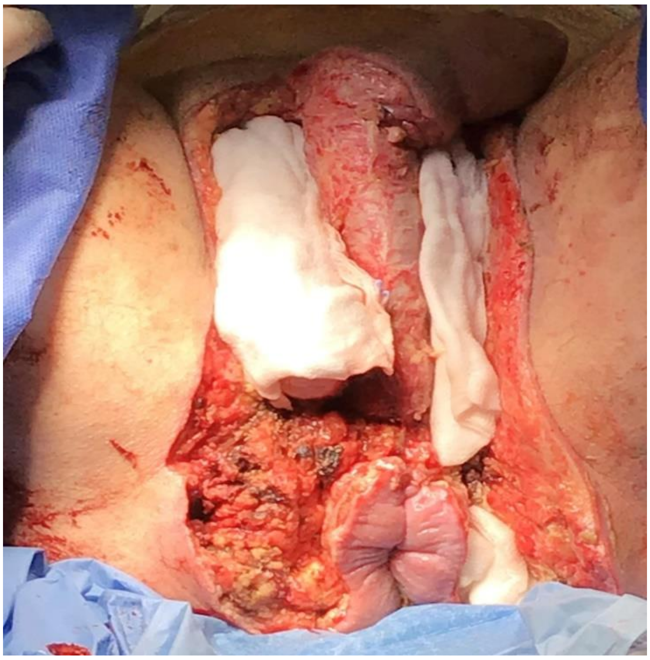

Fig. 1b

Fig. 1c

Fig. 1d

Fig. 1: Li-ESWT for secondary management of Fournier`s gangrene – stimulation of wound healing after failure of closure with skin flaps

a) Initial presentation of patient with severe Fournier`s gangrene (acute necrotizing fasciitis) in the genital and perineal area.

b) Radical excision of the involved tissue finally resulting to a wound area of 74.9 cm^2.

c) Secondary healing after closure of the defect with skin flaps with an open wound area of 35.3 cm^2.

d) Closure of the wound 9 weeks (= 63 days) after Li-ESWT (2000 impulses, 3 Hz, 12 sessions) with a remaining wound area of 9.5 cm^2 corresponding to a re-epithelization speed of 0.41 cm^2/d.

Fig. 2a

Fig. 2b

Fig. 2c

Fig. 2: Li-ESWT for secondary management of Fournier`s gangrene – stimulation of primary wound healing prior to application of mesh-graft.

a) Situation after radical excision of the involved tissue with an open wound area 81.7 cm^2.

b) Significant closure of the wound with granulating tissue of the left testis after 9 weeks (=63 days) following Li-ESWT (2500 impulses, 4 Hz, 9 sessions) resulting to a remaining wound area of 40.8 cm^2. This corresponds to a re-epithelization speed of 0.65 cm^2/d.

c) Situation following placement of mesh-graft.

Table 1: Li-ESWT in the postoperative management of Fournier`s gangrene – Patients data and outcome

Indication	N	Energy flux density [mJ/mm^2]	Frequency [Hz]	Impulses per session	Sessions	Size of Lesion prior ESWT (cm^2)	Size of Lesion after ESWT (cm^2)	Time interval (d)	Re-epithelisation speed ($\Delta cm^2/d$)	Outcome
Case 1: Failure of primary skin flap	3	0.25	3	2000	12-15	18.7 30.3 35,3	8.6 6.8 9.5	42 56 63	0,24 0.42 0,41	Complete healing of secondary skin defect No surgery required
Case 2: Reduction of wound surface prior to mesh graft	2	0.25	3	2500	9	81,7 99.7	40,8 55.3	63 56	0,65 0.79	Significant reduction of wound surface Granulomatous tissue covering left testicle
Case 3: Restoration of resected tissue	3	0.25	3-4	3000	6-18	99.0 55.9 84.3	0,0 0.0 0.0	150 120 150	0,66 0.47 0.56	Complete healing of wound with restoration of local tissue (penile skin, scrotal skin Granulomatous tissue covering the wound

Case Series 3: Based on our good experiences with the case series 1 and 2, we treated further three patients with complete necrosis of the scrotal and penile skin requiring radical excision primarily with Li-ESWT according to the protocol (Fig.3, Fig. 4). Obviously, there was not much tissue available for adequate plastic surgery of penile and scrotal skin.

TREATMENT PROTOCOL USING LOW-ENERGY SHOCK WAVE THERAPY:

All patients were treated with Li-ESWT using the electromagnetic device Duolith SD1 ultra (Storz-Medical, Taegerwilen, Switzerland). This device delivers focused shock waves to human tissue generated by an electromagnetic cylinder and focused by a paraboloid reflector. The -6dB lateral focal zone depends on the energy setting and was 4 mm resulting to a focus volume of 0.5 cm^3. The positive shock wave pressure was 24 MPa at a energy density of 0.25 mJ/mm^2. The focal depth can be regulated by use off different coupling devices (i.e. stand-offs). We used the stand-off which we use for treatment of erectile dysfunction and Peyronie`s disease, which has a depth of 5-8 mm. We applied three times weekly (Monday, Wednesday, Friday) 2000-3000 shock waves at 3-4 Hz with an energy flux density of 0.25 mJ/mm^2 distributed equally on the rims of the wound (Fig. 3a; Table 1). Low-intensity shock wave therapy is defined to use shock waves at an energy flux density of lower than 35 mJ/mm^2 per impulse.[14] The treatment was well tolerated with no need of anesthesia or analgesia.

PLANIMETRIC ASSESSMENT OF RE-EPITHELIZATION

Based on the existing picture taken at several times before and after Li-ESWT we performed planimetric assessment of the wound area at the respective time. This allowed us to calculate the re-epithelization speed (cm^2/d) = Wound area prior ESWT – Wound area at end of treatment / days of treatment and observation (Table 1). These results were compared with experimental and clinical data in the literature.

Results

Case Series 1: In three cases, we treated secondary healing of skin-flaps with an open wound area ranging from 18.7 to 35.3 cm^2. All wounds showed a dramatic progress in the healing process with almost complete healing by the local skin (open wound surface 6.8 to 9.5 cm^2 after 7-9 weeks (Fig. 1) corresponding to a re-epithelization speed of 0.24 to 0.42 cm^2/d. No further surgical procedure was required.

Case Series 2: Both cases (initial wound area 81.7 and 99.7 cm^2) responded very well on the Li-ESWT-treatment starting with intensive granulation tissue covering the wound after 8-9 weeks with significant reduction of the surface from the periphery by the local skin (wound area 40.8 and 55.3 cm^2) corresponding to a re-epithelization speed of 0.65 and 0.79 cm^2/d. At that stage we placed a mesh-graft, which healed in without any further complications (Fig. 2c) and was much smaller than for the initial size of the wound.

Case Series 3: Finally, we were able to close all three open wounds (initial wound area 55.9 to 99.0 cm^2) completely only by use of Li-ESWT. This wound repair did not occur just as fibrous tissue. It started with decrease of the wound area from the rims and formation of granulation tissue covering the wound (Fig, 4b) respectively cleaning of the wound (Fig. 3b). Further on, the excised scrotal skin was completely restored as scrotal tissue and the penile skin accordingly providing an optimal cosmetic result after 5 and 9 months (Fig. 4c, 4d). The patient in Manila received only 6 sessions of Li-ESWT leading basically to the same result (Fig. 3c). This corresponded to a re-epithelization speed ranging from 0.47 to 0.66 cm^2/d.

In summary, the observed re-epithelization speed varied between 0.24 and 0.79 cm^2/d depending mostly on the size of the defect when starting the treatment. (Table 1).

Fig. 3a

Fig. 3b

Fig. 3c

Fig. 3: Li-ESWT for secondary management of Fournier`s gangrene -Technique of LI-ESWT and follow-up of patient treated exclusively by Li-ESWT.

a) Application of 2000-3000 Shock Waves on the rim of the wound using the handpiece of the Duolith SD (Storz-Medical, Taegerwilen, Switzerland) with 0.25 mJ/mm^2 at 3-4 Hz three days weekly. The wound area was 99.0 cm^2.

b) Significant improvement of the wound healing after 6 weeks, Complete cleaning of the wound.

c) Complete closure of the wound 5 months (=150 days) corresponding to a re-epithelization speed of 0,82 cm^2/d) after Li-ESWT (3000 impulses, 4 Hz, 6 sessions).

Fig. 4a

Fig. 4b

Fig. 4c

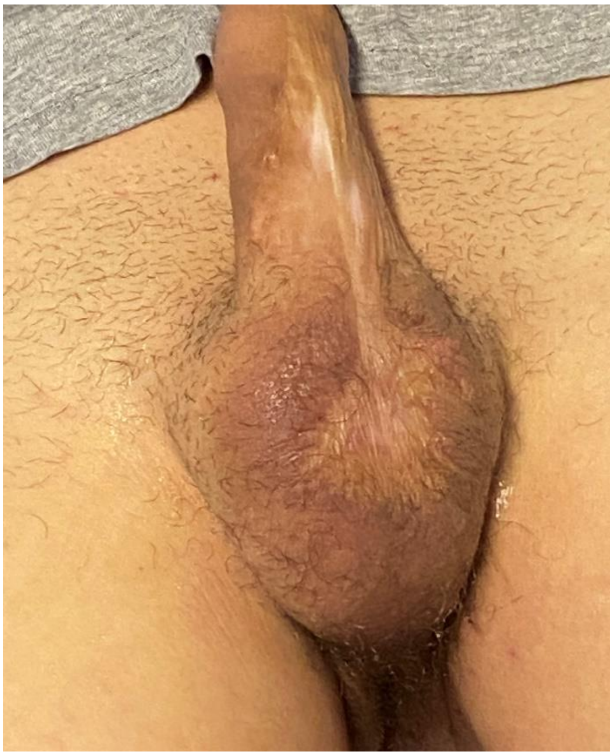

Fig. 4d

Fig. 4: Li-ESWT for secondary management of Fournier`s gangrene - Li-ESWT as single management of wound healing following radical excision of infected tissue after Fournier`s gangrene with long-term result.

a) Radical excision of the involved tissue with an open area of 84.3 cm^2.

b) Intermediate phase after 6 weeks with closure of the wound by granular tissue

c) Complete restoration of the wound by scrotal and penile tissue following 4 months (=120 days) after Li-ESWT (3000 impulses, 4 Hz, 18 sessions) corresponding to a re-epithelization speed of 0.70 cm^2/d. No surgery required at all.

d) Final cosmetic result after 9 months with almost normal appearance of scrotal and penile skin.

Discussion

There have been several attempts to improve the wound healing after complete surgical excision in case of Fournier`s gangrene: A more recent comparative case series suggested benefit for use of hyperbaric oxygen therapy in sixteen patients compared to twelve cases without use of such therapy in terms of reduced mortality and fewer debridement.[3]

A low-quality RCT with 30 patients found that use of honey-soaked dressings resulted in a shorter hospital stay (28 vs. 32 days) than dressing soaked with Edinburgh solution of lime.[7] No evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene was found.

Already in 1990, Haupt and Chapvil examined the effect of shock waves on wound healing in an in-vivo porcine model using the Dornier XL1-experimental lithotripter and concluded that low energy levels (14 vs. 18 kV) coincided with an increased vascularization.[11] More than ten years later, in 2007 Schaden et al. initiated the first clinical trials on Li-ESWT for wound healing.[12]

In the meantime, several experimental and clinical studies documented an accelerated tissue repair and regeneration in various wounds following Li-ESWT.[16-21] However, the complete biomolecular mechanism by which this treatment modality exerts its therapeutic effects remains still unclear. Shock waves' primary physical effect is believed to be via mechanotransduction leading to cellular activation and downstream signaling. It has become evident, that only low-intensity (energy flux density < 35 mJ/mm^2) is required.[16] Experimentally, ESWT's effects on osseous, connective tissue and wound healing via various mechanisms of action have been reported both in the literature. Potential mechanisms include initial neovascularization with ensuing durable and functional angiogenesis. Furthermore, recruitment of stem cells, stimulated cell proliferation and differentiation, and anti-inflammatory and antimicrobial effects as well as suppression of nociception are considered important facets of the biological responses to therapeutic shock waves.[17-21,23]

Early studies of the group of Mittermayr and Schaden tried to evaluate the effect of Li-ESWT on "standardized" wounds using the donor situs of skin-grafts.[15] They found a "faster complete epithelialization" with ESWT compared to the placebo group. The same was observed in clinical studies treating diabetic foot ulcers.[24] However, until now no *re-epithelization speed* has been calculated in the literature. There are several experimental trials dealing with wound healing and re-epithelization, but none of the studies used ESWT as a treatment option.[6,26-28] We were able to calculate the re-epithelization speed based on the data provided by the articles (Table 2). However, such data cannot be compared with clinical data.

Table 2: Re-epithelization effects and wound-healing rates in animal studies

Author	Model	Lesion	Treatment groups	Wound area at day 0 (cm^2)	Wound area at final evaluation (cm^2)	Time interval (d)	Re-epithelization speed ($\Delta cm^2/d$)	Comment
Negm et al.[26] 2022	Wistar Rats	Excisional full thickness skin wound	Control Betadine-cream Rhoifolinn rich fraction-gel	1.08 1.2 1.1	0.3 0.01 0	10 10 10	0,08 0.11 0.11	Treatment groups with inflammatory activity
Rowland et al.[27] 2022	Wild type mouse	Skin punch biopsy	Male Female	0.36 0.36	0.22 0.14	5 5	0.03 0.04	Females heal faster
Munoz et al.[6] 2023	Guinea pig	Circular burn injury	Control Honey-impregnated gauze	0.78 0.78	n.a. n.a.	n.a. n.a.	n.a. n.a.	Use of re-epitheliazation score
Le Kuiai et al.[28] 2018	Diabetic mice Normal mice	Circular punch	Control SJHY-formula Control SJHY-formula	0.28 0.28 0.28 0.28	0.09 0.06 0.03 0.02	10 10 10 10	0.019 0.022 0,025 0,026	SJHY-Formula works only in diabetic mice

Table 3: Comparison of Re-epithelization effects and wound-healing rates in clinical studies

Author	Lesion	Treatment groups	Wound area at day 0 (cm^2)	Wound area at day 7 (cm^2)	Difference of Wound area (cm^2)	Re-epithelization speed ($\Delta cm^2/d$)	Comment
Ottomann et al.[24] 2010	Skin graft donor site of trauma patients	Defocused shock wave therapy 0.1.mJ/mm^2 DermaGold, MTS	n.a.	n.a.	n.a.	n.a.	Significant faster healing of the donor site 13,9 versus 16,7 d
Dymarek et al.[29] 2024	Pressure ulcers Grade II and III	Radial ESWT (2 sessions)	13.5	7,3	6.2	0.9	Major skin cells, Keratinocytes, Fibroblasts are mechanosensitive

There are only two recent clinical studies: Ottomann et al.[24] presented a randomized trial including 28 patients with acute traumatic wounds and burns requiring skin grafting of which 13 patients received standard topical the to graft donor sites with and 15 without defocused extracorporeal shock wave therapy (ESWT, 100 impulses/cm^2 at 0.1 mJ/mm^2), They were able to show, that with a single treatment of ESWT, the donor site healed significantly faster (13.9 vs. 16.7 d). However, there are no data on the size of the wounds. Dymarek et al., presents data concerning re-epithelization following ESWT for pressure ulcers. [29] However, the interval between the second ESWT-session and evaluation was only seven days resulting to a decrease of the wound area from 13.5 to 7.2 cm^2 corresponding to a re-epithelization speed of 0.9 cm^2/d. We observed a re-epithelization speed of maximal 0.79 cm^2/d. Obviously, further studies are necessary to determine the base-lines for the re-epithelization speed as an instrument to compare different approaches to wound healing.

Even, if still only based on case studies, our experiences with complete restoration of different types of skin (i.e. perineal, penile, scrotal) following extensive tissue resection due to Fournier`s gangrene suggests, that the underlying mechanism for this is related to a stimulation of stem cells. Unlike the formation of superficial scar-like repair, when using skin grafts.[4] Stem cell formation induced by shock waves has been already shown experimentally in different animal models, such as pelvic floor trauma or erectile dysfunction.[30-32] A recent review article describes also possible clinical indications, such as cardiomyopathy. However, the authors did not mention skin repair in their article. In our opinion, the skin offers the unique opportunity to watch the progress of healing and tissue restauration as a model for the new concept of regenerative medicine.

However, further studies are necessary to confirm these anecdotal observations. Due to the low incidence of Fourniers`s gangrene further multi-center studies should be initiated. Like in other indications of wound healing, these studies have to focus on treatment parameters (ie. number of impulses, energy flux density, number of sessions), but also on comparison of Li-ESWT with existing therapeutic modalities. Herein, the calculation of re-epithelization speed may become a crucial instrument

Conclusions

The positive effect of Li-ESWT in the postoperative management of Fournier`s gangrene seems to be evident and could be reproduced in two continents. There are no negative side effects. Based on the obvious findings of complete restoration of different kinds of skin (i.e. perineal, penile, and scrotal) the underlying mechanism might be stem cell stimulation by mechano-transduction induced by low-intensity shock wave therapy. Nevertheless, further studies are necessary to confirm our casuistic findings and to determine the optimal treatment parameters of this rare disease. Here the re-epithelization speed may become an important parameter.

Conflict of Interest:

None

Acknowledgements:

None

References:

1. Eke N. Fournier's gangrene: a review of 1726 cases. Br J Surg. 2000 Jun;87(6):718-28. doi: 10.1046/j.1365-2168.2000.01497.x. PMID: 10848848.

2. Jennifer Kranz, Riccardo Bartoletti, Franck Bruyère, et al. European Association of Urology Guidelines on Urological Infections: Summary of the 2024 Guidelines. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2024.03.035

3. Singh A, Ahmed K, Aydin A, Khan MS, Dasgupta P. Fournier's gangrene. A clinical review. Arch Ital Urol Androl. 2016 Oct 5;88(3):157-164. doi: 10.4081/aiua.2016.3.157. PMID: 27711086.

4. Suda S, Hayashida K. Crafting Contours: A Comprehensive Guide to Scrotal Reconstruction. Life (Basel). 2024 Feb 4;14(2):223. doi: 10.3390/life 14020223. PMID: 38398732; PMCID: PMC10890180.

5. Haidari M, Nazer MR, Ahmadinejad M, Almasi V, Khorramabadi MS, Pournia Y. Honey in the treatment of Fournier's gangrene as an adjuvant: a cross- sectional study. J Pak Med Assoc. 2014 May;64(5):571-3. PMID: 25272547.

6. Muñoz M, Del Sol M, Vásquez B. Antibacterial and wound-healing action of Ulmo honey (*Eucryphia cordifolia*) of differing degrees of purity. Front Vet Sci. 2023 May 12;10:1172025. doi: 10.3389/fvets.2023.1172025. PMID: 37252390; PMCID: PMC10213365.

7. Mladenov A, Diehl K, Müller O, von Heymann C, Kopp S, Peitsch WK. Outcome of necrotizing fasciitis and Fournier's gangrene with and without hyperbaric oxygen therapy: a retrospective analysis over 10 years. World J Emerg Surg. 2022 Aug 5;17(1):43.

8. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet. 1980 Dec 13;2 (8207):1265-8. doi: 10.1016/s0140-6736(80)92335-1. PMID: 6108446.

9. Fuchs G, Miller K, Rassweiler J, Eisenberger F. Extracorporeal shock-wave lithotripsy: one-year experience with the Dornier lithotripter. Eur Urol. 1985;11(3):145-9. doi: 10.1159/000472479. PMID: 4029228.

10. Rompe JD, Hopf C, Nafe B, Burger R. Low-energy extracorporeal shock wave therapy for painful heel: a prospective controlled single-blind study. Arch Orthop Trauma Surg. 1996;115(2):75-9. doi: 10.1007/BF00573445. PMID: 9063856.

11. Haupt G, Chvapil M. Effect of shock waves on the healing of partial-thickness wounds in piglets. J Surg Res. 1990 Jul;49(1):45-8. doi: 10.1016/0022-4804(90)90109-f. PMID: 2359293.

12. Haupt G, Haupt A, Ekkernkamp A, Gerety B, Chvapil M. Influence of shock waves on fracture healing. Urology. 1992 Jun;39(6):529-32. doi: 10.1016/0090-4295(92)90009-l. PMID: 1615601.

13. Schaden W, Thiele R, Kölpl C, Pusch M, Nissan A, Attinger CE, Maniscalco-Theberge ME, Peoples GE, Elster EA, Stojadinovic A. Shock wave therapy for acute and chronic soft tissue wounds: a feasibility study. J Surg Res 2007;143(1): 1-12.

14. Skov-Jeppesen SM, Petersen NA, Yderstraede KB, Jensen BL, Bistrup C, Lund L. Low-Intensity Extracorporeal Shockwave Therapy (LI-ESWT) in Renal Diseases: A Review of Animal and Human Studies. Int J Nephrol Renovasc Dis. 2023 Feb 6;16:31-42. doi: 10.2147/IJNRD.S389219. PMID: 36778197; PMCID: PMC9912820.

15. Mariotto SC, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, Russo S, Suzuki H. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric Oxide 2005; 12(2): 89-96.

16. Mittermayr R, Antonic V, Hartinger J, Kaufmann H, Redl H, Téot L, Stojadinovic A, Schaden W. Extracorporeal shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy. Wound Repair Regen. 2012;20 (4):456-65.

17. Kisch T, Wuerfel W, Forstmeier V, Liodaki E, Stang FH, Knobloch K, Mailaender P, Kraemer R. Repetitive shock wave therapy improves muscular microcirculation. J Surg Res 2016; 201(2):440-445.

18. Serizawa F, Ito K, Matsubara M, Sato A, Shimokawa H, Satomi S. Extracorporeal shock wave therapy induces therapeutic lymphangiogenesis in a rat model of secondary lymphoedema. Eur J Vasc Endovasc Surg 2011; 42(2):254-260.

19. Frairia R, Berta L. Biological effects of extracorporeal shock waves on fibroblasts. A review. Muscles Ligaments Tendons J 2011 1(4): 138-147.

20. Holsapple JS, Cooper B, Berry SH, Staniszewska A, Dickson BM, Taylor JA, Bachoo P, Wilson HM. Low Intensity Shockwave Treatment Modulates Macrophage Functions Beneficial to Healing Chronic Wounds. International Journal of Molecular Sciences. 2021; 22(15):7844. https://doi.org/10.3390/ijms22157844

21. Basoli V, Chaudary S, Cruciani S, Santaniello S, Balzano F, Ventura C, Redl H, Dungel P, Maioli M. Mechanical Stimulation of Fibroblasts by Extracorporeal Shock Waves: Modulation of Cell Activation and Proliferation Through a Transient Proinflammatory Milieu. Cell Transplant. 2020 Jan-Dec;29:963689720916175. doi: 10.1177/0963689720916175. PMID: 32326741; PMCID: PMC7586264.

22. Rassweiler JJ, Scheitlin W, Goezen AS, Rassweiler-Seyfried MC. Low-energy shockwave therapy in the management of wound healing following Fournier's gangrene. Eur Urol Open Sci 2022;45: 8-11.

23. Rassweiler J, Ringeisen M, Knobloch K, Schaden W. Efficacy and Theoretical Basis of Low-Intensity Shock Wave Therapy in the Management of Different Forms of Wound Healing: Own Experiences and a Review of the Literature, Medical Research Archives, [online] 2023; 11(8). https://doi.org/10.18103/mra.v 11i8.4394

24. Ottomann C, Hartmann B, Tyler J, Maier H, Thiele R, Schaden W, Stojadinovic A. Prospective randomized trial of accelerated re-epithelization of skin graft donor sites using extracorporeal shock wave therapy. J Amer Coll Surg 2010; 05.012; ISSN 1072-7515/10/; doi:10.1016

25. Wang CJ, Cheng JH, Kuo YR, Schaden W, Mittermayr R. Extracorporeal shockwave therapy in diabetic foot ulcers. Int J Surg. 2015 Dec;24(Pt B):207-9. doi: 10.1016/j.ijsu.2015.06.024. Epub 2015 Jun 12. PMID: 26079500.

26. Negm WA, El-Kadem AH, Elekhnawy E, Attallah NGM, Al-Hamoud GA, El-Masry TA, Zayed A. Wound-Healing Potential of Rhoifolin-Rich Fraction Isolated from *Sanguisorba officinalis* Roots Supported by Enhancing Re-Epithelization, Angiogenesis, Anti-Inflammatory, and Antimicrobial Effects. Pharmaceuticals (Basel). 2022 Jan 31;15(2):178. doi: 10.3390/ph15020178. PMID: 35215291; PMCID: PMC8874642.

27. Rowland MB, Moore PE, Bui C, Correll RN. Assessing wound closure in mice using skin-punch biopsy. STAR Protoc. 2023 Mar 17;4(1):101989. doi: 10.1016/j.xpro.2022.101989. Epub 2023 Jan 4. PMID: 36602903; PMCID: PMC9826969.

28. Kuai L, Zhang JT, Deng Y, Xu S, Xu XZ, Wu MF, Guo DJ, Chen Y, Wu RJ, Zhao XQ, Nian H, Li B, Li FL. Sheng-ji Hua-yu formula promotes diabetic wound healing of re-epithelization via Activin/Follistatin regulation. BMC Complement Altern Med. 2018 Jan 29;18(1):32. doi: 10.1186/s12906-017-2074-8. PMID: 29378560; PMCID: PMC5789635.

29. Dymarek R, Kuberka I, Walewicz K, Taradaj J, Rosińczuk J, Sopel M. Is Shock Wave Application Effective on Various Chronic Wounds in the Geriatric Population? Preliminary Clinical Study. Clin Interv Aging. 2024 Apr 30;19:665-679. doi: 10.2147/CIA.S448298. PMID: 38706636; PMCID: PMC11069372.

30. Schuh CM, Heher P, Weihs AM, Banerjee A, Fuchs C, Gabriel C, Wolbank S, Mittermayr R, Redl H, Rünzler D, Teuschl AH. In vitro extracorporeal shock wave treatment enhances stemness and preserves multipotency of rat and human adipose-derived stem cells. Cytotherapy. 2014 Dec;16(12): 1666-78. doi: 10.1016/j.jcyt.2014.07.005. Epub 2014 Aug 28. PMID: 25174738.

31. Lin G, Van Kuiken M, Wang G, Banie L, Tan Y, Zhou F, Wang Z, Chen Y, Zhang Y, Lue TF. Microenergy acoustic pulse therapy restores function and structure of pelvic floor muscles after

simulated birth injury. Transl Androl Urol 2022;11 (5): 595-605

32. Shin D, Jeon SH, Tian WJ, Kwon EB, Kim GE, Bae WJ, Cho HJ, Hong SH, Lee JY, Kim SW. Extracorporeal shock wave therapy combined with engineered mesenchymal stem cells expressing stromal cell-derived factor-1 can improve erectile dysfunction in streptozotocin-induced diabetic rats. Transl Androl Urol. 2021;10(6):2362-2372.

33. Kou D, Chen Q, Wang Y, Xu G, Lei M, Tang X, Ni H, Zhang F. The application of extracorporeal shock wave therapy on stem cells therapy to treat various diseases. Stem Cell Res Ther. 2024 Aug 26;15(1):271. doi: 10.1186/s13287-024-03888-w. PMID: 39183302; PMCID: PMC11346138.

