SPARK OF EVIDENCE

Technology Assessment "Wound Care" dermagold100 MTS 2017

# Technology Assessment
# „Wound Care“ Dermagold 100™
# MTS 2017

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# 1. Introduction: Acute and chronic wounds, the purpose of shock waves in wound healing

## 1.1. Classification of wounds

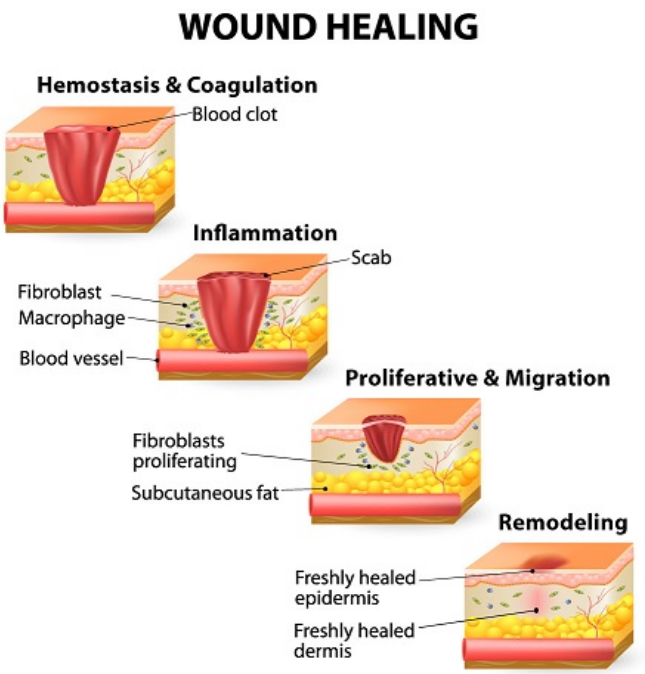
Acute wounds are caused exogenously by traumatic (e.g. mechanical, chemical, thermical) or iatrogenic (e.g. surgical) injury. In general, they are sharply limited and heal within short time without major complications. If there is no progress in healing after more than 4 weeks, they are referred to as chronic wounds, which arise from disturbed wound healing processes due to other underlying diseases, like diabetes mellitus, venous diseases, circulation problems or disorders of the immune system. Chronic wound margins are imprecise and in the majority of cases they are infected. Chronic wounds have not completed the process of healing (restoring tissue loss and skin function), have not responded to initial treatment or persist despite appropriate care [12]. These wounds usually do not close without interferences and are sometimes resistant to healing interventions. Severe burns, diabetic foot ulcers (DFU), pressure ulcers or "bed sores," vascular ulcers, and complications of surgically created wounds commonly become chronic wounds because their etiologies impede healing, and they persist without proper medical care whereby especially elderly people are affected [2].

## 1.2. Skin structure and wound healing processes

The skin's functions are performed by three distinct tissue layers: a thin outer layer of cells called the epidermis, a thicker middle layer of connective tissue called the dermis, and an inner, subcutaneous layer. The outer layers of the epidermis are composed of flattened, cornified dead keratinocytes that form a barrier to water loss and microbe entry. These cells are derived from a basal layer of constantly dividing keratinocytes that lies next to the dermis. The epidermis does not contain nerves or blood vessels and obtains water and nutrients through diffusion from the dermis. The dermis is composed mostly of collagen fibers and some elastic fibers both produced by fibroblasts and, along with water and large proteoglycan molecules, makes up the extracellular matrix. This layer of the skin provides mechanical strength and a substrate for water and nutrient diffusion; it contains blood vessels, nerves, and cells involved in immune function, growth, and repair. The dermis also contains sweat glands, oil glands, and hair follicles. The subcutaneous layer is composed of adipocytes that form a thick layer of adipose tissue. [23]

Superficial wounds such as abrasions affect mainly the epidermis and are quickly healed by growth of new keratinocytes to cover the damaged skin. Partial-thickness skin loss involves the epidermis and dermis and requires more extensive healing, especially if the wound is large. Full-thickness skin loss involves penetration through the epidermis and dermis into the subcutaneous tissue and may expose muscle and bone. [2] Conclusively, wound healing involves multiple cell populations, the extracellular matrix and the action of soluble mediators such as growth factors and cytokines. Although the process of healing is continuous, it may be arbitrarily divided into four phases: (i) coagulation and haemostasis;

(ii) inflammation; (iii) proliferation / granulation; and (iv) wound remodelling with scar tissue formation / epithelialization [4]. These broad varieties of cellular events are dependent on fluent cell-to-cell communication between signalling molecules as well as on an adequate nutrient supply. Therefore, a re-establishment of a functional vasculature, sufficient blood supply and the activation of cellular regeneration processes are crucial for wound healing in the traumatized tissue [56]. This is where extracorporeal shock wave therapy (ESWT) comes into play and represents an innovative therapeutic tool of regenerative medicine by beeing growth-promotive at different cellular levels.




*(Figure taken from: https://dimensionaldermatology.com)*

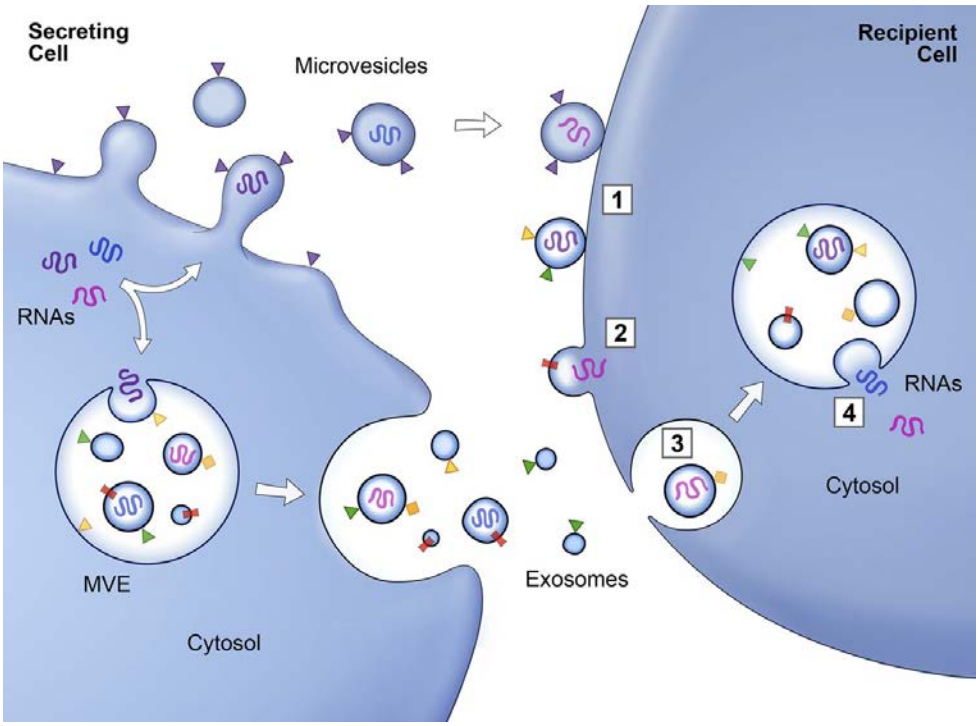
## 1.3. The purpose of shock wave technology and its biological mode of action

The original application of extracorporal shock waves in medicine was the destruction of kidney stones by lithotripsy in 1980. During this procedure the tissue is exposed to high accoustic energy and much effort was spent to investigate its potential side effects. In consequence, destructive but also regenerative effects were observed [7]. A dose-dependent effect was detected with high energy leading to more destructive effects and lower energy leading to more regenerative effects on the treated tissue [89]. In the early 1990s, extracorporeal shock wave effects on bone and soft tissues have led to indicating this treatment also for musculoskeletal disorders [7]. Since 2007, defocused shock waves were subjected to soft tissue indications with promising success [10,11]. Nowadays it is applied effectively as an adjunctive therapy for wound healing in combination with standard care procedures (debridement, dressings, skin grafts, nutritional support, infection control...). Chronic wounds, in particular, require a multidisciplinary approach.

After regnerative effects of shock waves became evident, scientists step by step discovered numerous elements playing a role in healing proceses. Although the precise biomolecular mechanisms of shock waves in tissues are still under investigation, it is most likely that the underlying principle of its effect can be based on a mechanical stimulation that becomes transformed into a cellular regeneration and growth-associated response. In recent years, the field of “mechanobiology” emerged in the scientific field and researchers began to analyze the cellular effects of physical stimuli and to elucidate this mechanotransduction by which cells and tissues adapt their molecular behaviour due to mechanical signals [12]. A

quantity of mechano-sensitive molecules and cellular components that are involved in mechanotransductive biochemical responses have already been identified, such as stretch-activated ion channels, caveolae, integrins, cadherins, growth factor receptors, myosin motors, cytoskeletal filaments, nuclei, extracellular matrix, and numerous other structures and signaling molecules [13]. It has been shown, that extracellular vesicles are released by mechanical shear stress and transfer miRNAs between cells [14,15]. New Evidence indicated that the mechanical stimulus of shock wave treatment causes exosome relase of cells *in vitro* and is translated into a direct biological response leading to endothelial proliferation and angiogenesis (presented and published at the 4th ISMST basic research meeting in Vienna 2016 by Tepeköylü C *et al.*, and the 20th international congress of the ISMST in San Sebastian 2017 by Graber M *et al.*) [14].

**Exosome release upon extracellular stimulus (SWT)**

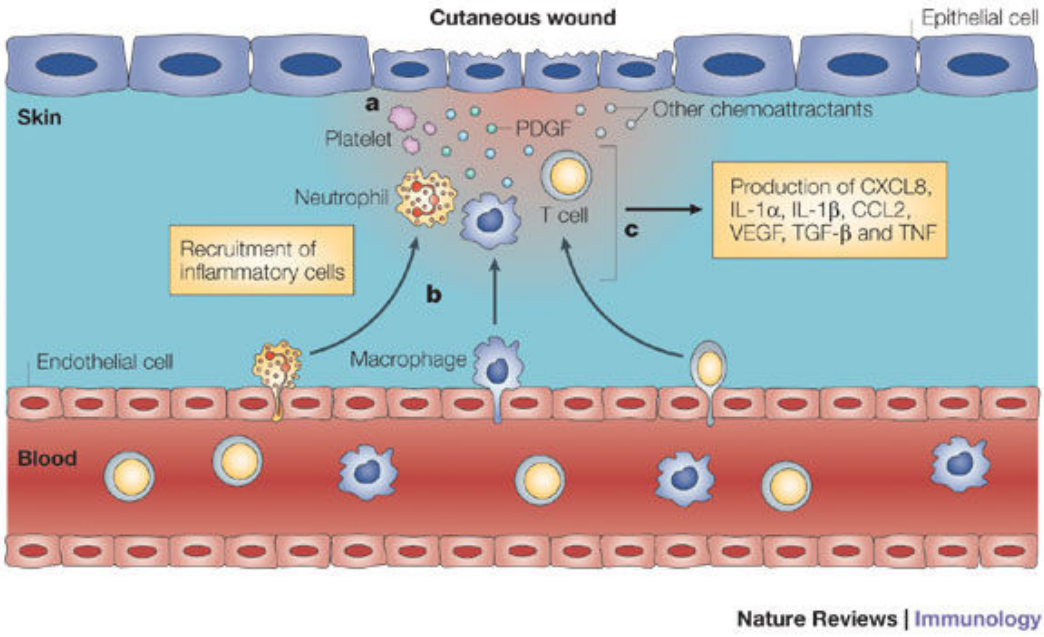



**Schematic of protein and RNA transfer by extracellular vesicles (Evs).** Membrane-associated (triangles) and transmembrane proteins (rectangles) and RNAs (curved symbols) are selectively incorporated into the intraluminal vesicle (ILV) of multivesicular endosomes (MVEs) or into microvesicles (MVs) budding from the plasma membrane. MVEs fuse with the plasma membrane to release exosomes into the extracellular milieu. MVs and exosomes may dock at the plasma membrane of a target cell (1). Bound vesicles may either fuse directly with the plasma membrane (2) or be endocytosed (3). Endocytosed vesicles may then fuse with the delimiting membrane of an endocytic compartment (4). Both pathways result in the delivery of proteins and RNA into the membrane or cytosol of the target cell. Fusion and endocytosis are only represented for exosomal vesicles, but plasma membrane–derived MVs may have similar fates. (Figure and caption taken from [15] ).

## 1.4. Mechanotherapy by shock waves; its biological relevance in wound healing

- **Inflammation** constitutes the first response during the process of wound healing. Normally, it is thought to be beneficial for the organism since it limits continuation of tissue damage by clearance of pathogens and recruits cells and factors that ultimately lead to full tissue regeneration and functionality [16]. Inflammation shifts to chronicization and becomes pathologic if the healing process is disturbed, often due to age and persisting comorbidities of the patients (diabetes, atherosclerosis, venous insufficiency, hypercholesterolemia...). Macrophages represent key mediators during inflammation as they regulate the onset, the amplification and resolution of the response. It was demonstrated that application of low energy shock waves could lower the pro-inflammatory and induce the anti-inflammatory profile in macrophages and altered the expression of cytokines and chemokines, like cyclophilin A, interleukins-6, -10 and -1β and of immune-receptors like the TLR3 (toll-like receptor 3) and other players [17–21]. Furthermore, in *in vivo* studies, shock waves reduced leucocyte and macrophage infiltration into isograft tissue and decreased the corresponding macrophage-derived inflammatory protein response (MIP-1 α and β), pointing on an anti-inflammatory mechanism of shock waves [22,23].

**Inflammatory processes during wound healing**



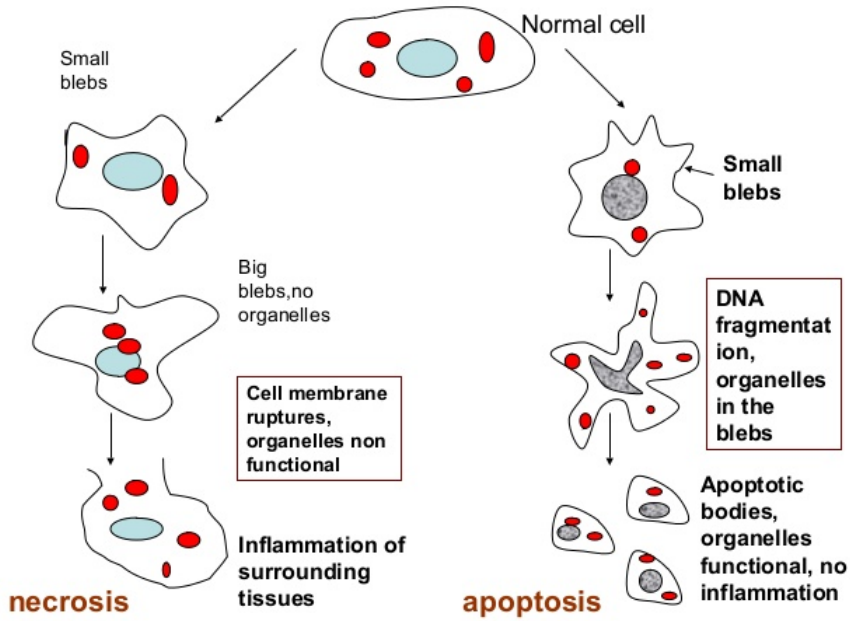

*(Figure taken from: [24])*

- **Infection** of chronic wounds is a major challenge during the treatment of wounds. Microbial colonization maintains the inflammation and impairs the process of healing. Shock waves were reported to have an bactericidal effect and to be able to reduce the bacterial burden of the affected tissue [25–28]**.** A further positive beneficial aspect of SWT is

that it increases the number of microvessels and improves the systemic delivery of antibiotics to the infected wound.

- **Apoptosis and necrosis** are known to have a high impact on regenerating tissue. Apoptotic cells can produce harmful signals that have a profound influence on neighboring cells and tissues linked to numerous pathologies. Necrotic cells release cellular contents and factors into the extracellular space which cause inflammation and further cell death. [29] In several studies it was demonstrated, that shock wave treatment decreases cellular apoptosis and can reduce necrosis of wounds [19,30–32].

**Cellular necrosis or apotosis pathways**

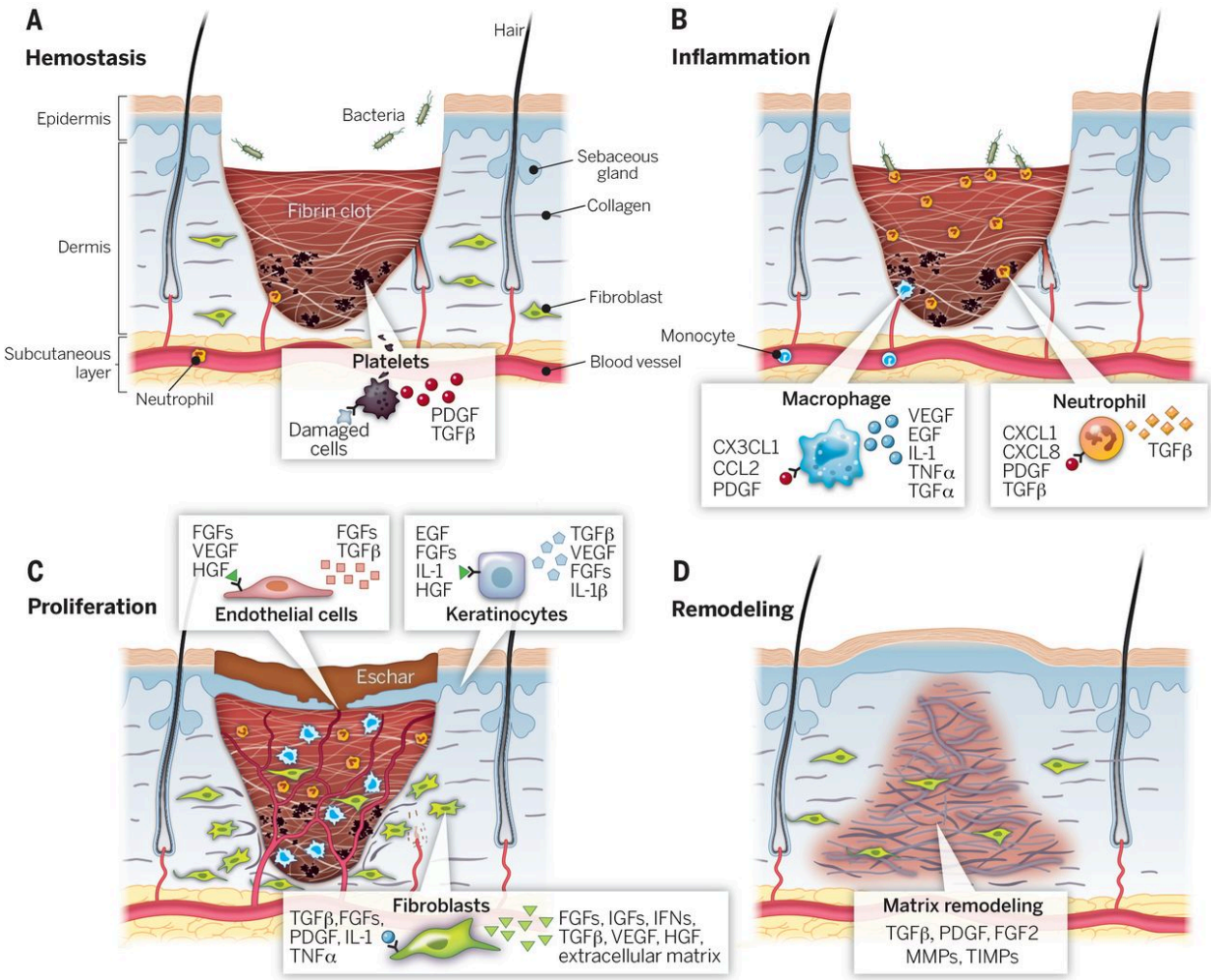



*(from: https://www.slideshare.net/norazhaniazmi/mechanism-cell-deaths)*

- **Tissue remodelling and neovascularization:** Re-establishment of a functional vasculature is the most critical determinant of restored tissue structure and function in wound healing, which largely occurs via angiogenesis, endothelial sprouting and vasculogenesis [5,6,20,33–35]. As the wound starts to heal, cells proliferate and build granulation tissue which is strongly permeated by capillaries. Later on, in the course of epithelialization, scar tissue is formed. Shock wave treatment (SWT) was shown to accelerate granulation and reepithelialization, and to reduce scar formation [20,36–39]. SWT increased the overall blood circulation of affected areas and stimulated cutaneous and muscular microcirculation [31,32,40–42]. In this respect, shock waves proved to be highly effective and beneficial, since treatment induced recruitment of endothelial progenitor cells and the expression of angiogenic factors like VEGF or TGF-β [43–45]. Nitric oxide (NO), a potent vasodilator, is another key player of shock wave-improved local blood flow and an important mediator of angiogenesis in the wounded area. NO became elevated upon SWT and enhanced tissue perfusion, partially due to the increased performance of nitric oxide synthase

(NOS) [16,46,47]. The primary mediator of angiogenic signaling -the vascular endothelial growth factor (VEGF)- and its corresponding receptor VEGF-R2, were also shown to be up-regulated upon ESWT treatment in numerous studies [48–50]. VEGF stimulated multiple components of the angiogenic cascade, capillary growth and promoted epithelialization and collagen deposition in the wound [51,52]. Furthermore, it was reported that ESWT has a positive effect on the expression of other important growth factors like BNDF (brain-derived neurotrophic factor), BMP (bone morphogenetic protein) and TGF-β (transforming growth factor), FGF-2 (fibroblast growth factor), IGF-1 (insulin growth factor) and PCNA (proliferating cell nuclear antigen) [53–58]. Hence, SWT strongly induces cascades of cell-proliferation and tissue re-growth [31]. Especially the activation of TGF-β1 and collagen type I and III, which are main factors involved in repair processes of connective tissues, confirmed a beneficial role of SWT in regeneration of the skin [54]. It stimulated proliferation and recruitment of fibroblasts by boosting extracellular matrix metabolism and connective tissue interaction [22,44,54]. Moreover, SWT led to recruitment, proliferation and differentiation of mesenchymal and penile progenitor cells [59–61]. The recent "bench to bedside"-study by Aschermann *et al.* demonstrated, that extracorporeal shock waves activate morphological changes and increase cell migration of keratinocytes. Cell-cycle regulatory genes were up-regulated and proliferation in fibroblasts was induced. This was accompanied by secretion of pro-inflammatory cytokines from keratinocytes, which are known to drive wound healing, and a pro-angiogenic activity of endothelial cells [62]. They demonstrated improved wound healing upon SWT in an open-label, single-arm study in patients with therapy-refractory chronic leg ulcers [63]. The toll-like receptors (TLRs), in addition to their established roles in immune defence system, have emerging roles in controlling homeostasis, injury and wound repair. The dsRNA-sensing receptor, TLR3, has been particularly implicated in such processes in several different tissues including the skin, intestine and liver, as well as in the control of reparative mechanisms in the brain, heart and kidneys, following ischemia reperfusion injury [64]. In 2013 and 2017, Hohlfeld *et al.* showed that SWT induced angiogenesis in endothelial cells specifically by stiumulation of TLR3 signaling [21,65].

**Detailed diagram of factors involved in phases of coutaneous wound healing**




*(Figure shared at: https://www.pinterest.de)*

- **Nociception and pain reduction** is another important part of wound care**.** Several multidisciplinary studies analyzed the role of ESWT in this respect and found that it has an analgesic effect and is able to suppress and relief pain which would be certainly beneficial for patients suffering from severe wounds and painful scars [5,16,30,39,66–72]**.**

More evidence from basic research and clinical studies concerning the role of ESWT in wound care is provided in detail in chapter **3. Body of literature** and listed in **5. References**.

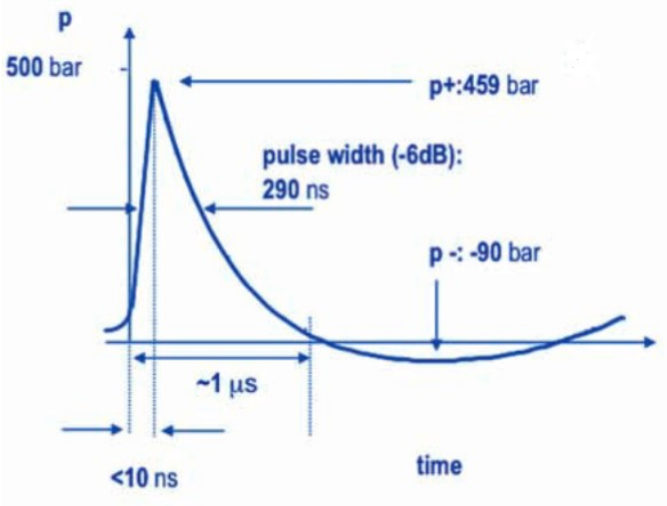
# 2. Shock wave technology basics and treatment methods

## 2.1. Definition

A shock wave is generated extracorporeally and defined by a transient pressure disturbance that propagates rapidly in three-dimensional space [73]. They are sonic pulses characterized by high peak pressure up to 500 bar or even more, rapid rise in pressure (<10 ns), short duration (<10ns) and a broad range of frequency [12]. The resulting energy is focused by concentrating reflectors and is noninvasively transmitted inside the body to induce therapeutic effects at a target area. A significant tissue effect is cavitation consequent to the negative phase of the wave propagation. Whether the biological response is triggered by mechanotransduction of the positive part of the shock wave and/or the negative/tensile pressure (cavitation) is not finally investigated to date. Although, cavitation is thought to be the force responsible for tissue damaging effects.

Shock waves used in medicine can be produced by different physical principles: electrohydraulic, electromagnetic, piezoelectric and pneumatic/radial. Electromagnetic and piezoelectric sources produce pressure waves which offer shock waves only in the focal area, whereas electrohydraulic systems produce shock waves outside of the focal area as well [5]. In wound care, typically a larger surface area needs to be treated with devices which deliver a wider wave. Therefore, electrohydraulic devices dominate publications in the scientific wound care field, which heads consist of a parabolic instead of an ellipsoid reflector resulting in a soft wide focus with a high energy density. The majority of orthopaedists use so-called radial shock wave devices with different physical characteristics. They generate pressure waves, not real shock waves [7]. It was shown that radial pressure waves produce significant cavitation and should be used with due caution in clinical practice [74]. They are not recommended for wound healing applications. Due to the different acoustic impedance of varying tissues, the aoustic energy becomes transformed into mechanical energy at the interface and stimulates biological regeneration processes in the affected areas [7].

**Pressure change over time during 1 shock wave** *(Graph taken from: [47])*



## 2.2. Manufacturers of electrohydraulic, defocused applicator systems suitable for wound indications

- **MTS Medical UG**, Dermagold 100™ (Konstanz, Germany) and **TRT**, Dermagold 100™ (MTS technology, Woodstock, USA)
- **Sanuwave health Inc.**, dermaPACE (Suwanee, USA)
- **HMT**, Evotron (Lengwil, Switzerland)
- **CellSonic Medical**, VIPP (India)

## 2.3. Shock wave treatment protocols for wound therapy

Shock waves in wound care are a relatively new physical therapy application. Therefore, treatment protocols still vary and have to be individualized and adapted to the patient and wound. Typical parameters to be modified are energy flux density, pulse frequency, number of sessions and duration/intervals of the treatment. When performing non-focused ESWT in soft tissues, it is important to operate within a low-energy range. As the energy increases, the effect switches from regeneration to destruction (lithotripsy). Energy flux density for soft tissue indications is typically in a range between 0.03-0.25 mJ/mm$^2$ (usually 0.1 mJ/mm$^2$) within a pulse frequency from 3 to 5 Hz (usually 4) and about 100-500 pulses/cm$^2$. On average, the duration is 5 - 10 minutes per session (up to 15 min) in 1-2 sessions per week and a total of 3-6 sessions [47,75]. The timepoints and beginning of the treatment are dependent on the severity and type of wound (partial-thickness skin loss or full-thickness skin loss; burns, ulcers, skin grafts…). Routinely, a sterile ultrasonic conducting gel is applied to the skin as contact medium and a sterile plastic drap or cellulose barrier is put between the wound and the ESWT applicator head.
To evaluate the efficacy of ESWT in wound healing correctly, a standardized process is useful. The progress in healing is assessed in terms of wound/ulcer size, degree of inflammation and stage of fibrosis, duration of healing and the time of complete epithelialization.

Detailed systematical reviews and references of treatment methods/protocols are listed in **3. Body of literature**, chapters **3.1 Reviews** and **3.5 Systematic reviews / metaanalysis**.

# 3. Body of literature / research evidence

## Basic research evidence for shock wave therapy in wound care:

### 3.1. Reviews

- **Antonic *et al.* 2011,** Evidence supporting extracorporeal Shock wave therapy for acute and chronic soft tissue wounds [5]
- **Mittermayr *et al.* 2012,** Extracorporeal Shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy [16]

### 3.2. Basic research studies using MTS technology (electrohydraulic)

- **Stojadinovic *et al.* 2008,** Angiogenic response to extracorporeal shock wave treatment in murine skin isografts [20] (TRT)
- **Davis *et al.* 2009,** Extracorporeal shock wave therapy suppresses the early proinflammatory immune response to a severe cutaneous burn injury [23] (TRT)
- **Kuo *et al.* 2009,** Extracorporeal shock-wave therapy enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of STZ-induced diabetes [76] (MTS)
- **Zins *et al.* 2010,** Comparative analysis of angiogenic gene expression in normal and impaired wound healing in diabetic mice: effects of extracorporeal shock wave therapy [77] (TRT)
- **Mittermayr et a. 2011,** Extracorporeal shock wave therapy (ESWT) minimizes ischemic tissue necrosis irrespective of application time and promotes tissue revascularization by stimulating angiogenesis [32] (MTS)
- **Sansone *et al.* 2012,** Early angiogenic response to shock waves in a three-dimensional model of human microvascular endothelial cell culture (HMEC-1) [78] (MTS. No full text available)
- **Weihs *et al.* 2014,** Shock wave treatment enhances cell proliferation and improves wound healing by ATP release-coupled extracellular signal-regulated kinase (ERK) activation [61] (TRT)
- **Antonic *et al.* 2015,** Extracorporeal Shock waves (ESW) Promote Proliferation and Differentiation of Keratinocytes In vitro-Histology and Immunohistochemistry [79] (TRT)

## 3.3. Basic research studies using MTS-equivalent technologies (electrohydraulic)

- **Haupt *et al.* 1990,** Effect of shock waves on the healing of partial thickness wounds in piglets [80] (Dornier lithotripter XL1)
- **Reichenberger *et al.* 2009,** Preoperative shock wave therapy reduces ischemic necrosis in an epigastric skin flap model [81] (Sanuwave)
- **Radu *et al.* 2011,** Shock wave treatment in composite tissue allotransplantation [82] (Sanuwave)
- **Reichenberger *et al.* 2011,** Comparison of extracorporal shock wave pretreatment to classic surgical delay in a random pattern skin flap model [83] (Sanuwave technology)
- **Reichenberger *et al.* 2011,** Optimal Timing of Shock wave treatment to protect Ischemic tissue [84] (Sanuwave)
- **Reichenberger *et al.* 2012,** Extracorporeal shock wave treatment protects skin flaps against ischemia-reperfusion injury [85] (Sanuwave)

## 3.4. Basic research studies using other/not specified technologies (piezoelectric, electromagnetic, radial)

- **Meirer *et al.* 2005,** Extracorporal shock wave may enhance skin flap survival in an animal model [86] (Dornier Epos)
- **Huemer *et al. et al.* 2007,** Comparison of the effectiveness of gene therapy with transforming growth factor-beta or extracorporal shock wave therapy to reduce ischemic necrosis in an epigastric skin flap model in rats [87] (Dornier Epos)
- **Abed *et al.* 2007,** Immunohistochemical evaluation of substance P and calcitonin gene-related peptide in skin and periosteum after extracorporeal shock wave therapy and radial pressure wave therapy in sheep [71]
- **Morgan *et al.* 2009,** Effects of extracorporeal shock wave therapy on wounds of the distal portion of the limbs in horses [88]
- **Silveira *et al.* 2010,** Effects of unfocused extracorporeal shock wave therapy on healing of wounds of the distal portion of the forelimb in horses [89]
- **Link *et al.* 2013,** Effect of unfocused extracorporeal Shock wave therapy on growth factor gene expression in wounds and intact skin of horses [90]
- **Kisch *et al.*, 2015** Remote effects of extracorporeal Shock wave therapy on cutaneous microcirculation [40]
- **Kisch *et al.*. 2015,** Fractionated Repetitive Extracorporeal Shock wave Therapy: A New Standard in Shock wave Therapy? [91]

## Clinical, evidence-based studies of shock wave therapy in patients with various wound care indications:

### 3.5. Systematic reviews / metaanalyses

- **Qureshi *et al.* 2011,** Shock wave therapy in **wound healing** [92]
- **Dymarek *et al.* 2014,** Extracorporeal shock wave therapy as an adjunct **wound treatment**: a systematic review of the literature [75]
- **Butterworth *et al.* 2015,** The effectiveness of extracorporeal shock wave therapy for the treatment of **lower limb ulceration**: a systematic review [93]
- **Wang J *et al.* 2015,** Extracorporeal shock wave therapy in **diabetic foot ulcers** [94] (review of clinical results)
- **Omar *et al.* 2017,** Extracorporeal shock wave therapy for the treatment of **chronic wound of lower extremity**: current perspective and systematic review [95]

### 3.6. Clinical studies using MTS technology (electrohydraulic)

- **Schaden *et al.* 2007,** Shock wave therapy for **acute and chronic soft tissue wounds**: a feasibility study [10] (TRT technology)
- **Dumfarth *et al.* 2008,** Prophylactic low-energy shock wave therapy improves **wound healing** after vein harvesting for coronary artery bypass graft surgery: a prospective, randomized trial [11] (MTS)
- **Wang *et al.* 2009,** Extracorporeal shock wave treatment for **chronic diabetic foot ulcers** [28] (MTS)
- **Larking *et al.*, 2010,** Randomized control of extracorporeal shock wave therapy versus placebo for **chronic decubitus ulceration** [96] (MTS)
- **Ottomann *et al.* 2010,** Prospective randomized trial of accelerated re-epithelization of **skin graft** donor sites using extracorporeal shock wave therapy (**traumatic wounds and burns**) [97] (MTS)
- **Stojadinovic *et al.* 2010, Combat Wound** Initiative program [98]
- **Wang *et al.* 2011,** Molecular changes in **diabetic foot ulcers** [36] (MTS)
- **Wolff *et al.* 2011,** The influence of comorbidities and etiologies on the success of extracorporeal shock wave therapy for **chronic soft tissue wounds**: midterm results [99] (TRT)
- **Ottomann *et al.* 2012,** Prospective randomized phase II Trial of accelerated reepithelialization of superficial **second-degree burn wounds** using extracorporeal shock wave therapy [38] (MTS)
- **Leal *et al.* 2014,** Shock wave medicine and **Leprosy** the ultimate challenge for skin regeneration by mechanotransduction (Abstract ISMST 2014) (MTS)
- **Saggini *et al.* 2015,** Extracorporeal Shock wave Therapy: An Emerging Treatment Modality for **Retracting Scars** of the Hands [39] (MTS)

## 3.7. Clinical studies using MTS-equivalent technology (electrohydraulic)

- **Saggini *et al.* 2008,** Extracorporeal shock wave therapy for management of **chronic ulcers** in the lower extremities [100] (HMT)
- **Arno *et al.* 2010,** Extracorporeal shock waves, a new non-surgical method to treat **severe burns** [101] (Sanuwave)
- **Wang *et al.* 2011,** Treatment of **diabetic foot ulcers**: a comparative study of extracorporeal shock wave therapy and hyperbaric oxygen therapy [31] (Sanuwave)
- **Fioramonti *et al.* 2012,** Extracorporeal shock wave therapy for the management of **burn scars** [37] (HMT Evotron)
- **Sultan-Bichat *et al.* 2012,** Treatment of **calcinosis cutis** by extracorporeal shock-wave lithotripsy [102] (EDAP TMS, Sonolith)
- **Jae Jung *et al.* 2014**, Outcomes of Ultrasound-Guided Extracorporeal Shock wave Therapy for **Painful Stump Neuroma** [103] (HMT, Evotron)
- **Wang *et al.* 2014,** Long-term outcomes of extracorporeal shock wave therapy for **chronic foot ulcers** [104] (Sanuwave)
- **Aschermann *et al.* 2017,** Extracorporal Shock waves Activate Migration, Proliferation and Inflammatory Pathways in Fibroblasts and Keratinocytes, and Improve Wound Healing in an Open-Label, Single-Arm Study in Patients with Therapy-Refractory **Chronic Leg Ulcers** [105] (CellSonic Medical technology)
- **A clinical trial by Sanuwave health inc. is currently under FDA approval:** (https://clinicaltrials.gov/ct2/show/NCT01824407?term=dermaPACE&rank=2) *"A Comparison of the dermaPACE® (Pulsed Acoustic Cellular Expression) Device in Conjunction With Standard of Care Versus Standard of Care Alone in the Treatment of Diabetic Foot Ulcers"*

## 3.8. Clinical studies using other technologies (piezoelectric, electromagnetic, radial)

- **Moretti *et al.* 2009,** The management of **neuropathic ulcers** of the **foot in diabetes** by shock wave therapy [106]
- **Omar *et al.* 2014,** Efficacy of shock wave therapy on **chronic diabetic foot ulcer**: a single-blinded randomized controlled clinical trial [107]
- **Jeppesen *et al.* 2016,** Extracorporeal shock wave therapy in the treatment of **chronic diabetic foot ulcers**: a prospective randomised trial [108]
- **Saito *et al.* 2016,** Extracorporeal Shock wave Therapy for Digital **Ulcers of Systemic Sclerosis**: A Phase 2 Pilot Study [72]
- **Soo Cho *et al.* 2016,** Effect of extracorporeal shock wave therapy on **scar pain** in **burn** patients [66]
- **Zaghloul *et al.* 2016,** Effect of Extracorporeal Shock wave Therapy on **Post Burn Scars** [109]

# 4. Discussion of efficacy and safety

## 4.1. Potential side effects of shock wave therapy

Usage of SWT in studies treating soft tissue indications like wound healing is considered as overall safe in the experts` community. Application of low to medium energy with focused or defocused generator heads and electrohydraulic or electromagnetic source is generally well tolerable in the treatment of cutanous wounds. Importantly, radial pressure waves are not recommended for wound applications. The side effects of radial / pneumatically generated pressure waves harbour considerable risk potential. Radial pressue waves are mainly used in orthopedics, where about 70 % of all physicians use pneumatic devices. In 2002, Haake *et al.* performed a study about side effects in the treatment of tennis elbow with ESWT. In all, 399 ESWT and 402 placebo treatments were analysed. More side-effects were documented in the ESWT group than in the placebo group. Most frequently, transitory reddening of the skin (21.1%), pain (4.8%) and small haematomas (3.0%) were found [110]. Some manufacturers report about skin irritations, reddening or swelling around the treated area, which goes away after a short period of time. Complications are rather known from high-energy shock wave treatments like lithotripsy, where in some cases deleterious effects like injury of inner organs (e.g. kidney, liver, pancreas, colon, spleen) have been reported, although very rarely [111].

Side effects are most likely related to the tensile / negative proportion of the shock wave. The patented shock wave technology of MTS mainly generates positive energy with very low cavitation. Accordingly, there are no reports about such unwanted side effects or negative feedback from physicians using MTS devices. Generally spoken, shock waves are safe and free from side effects when using the right technology and applying them accurately. Especially low-energy, defocused shock waves are most suitable for wound indication and can be considered harmless as none of the above mentioned studies report any adverse effects. SWT treatment in wound care can be characterized as non-invasive, mostly painless and safe. [16,75]

## 4.2. The benefits of shock wave therapy

The large body of literature and the substantial supporting clinical evidence that are already existing in the medical field of wound therapy now stongly suggest that shock waves should be used as an adjunct therapy in chronic and acute soft tissue wound care. Shock waves showed repruducible results in enhancing vascularization, reepithelialization and granulation of the treated tissue, thereby significantly shortening the time of healing. Furthermore, the therapy reduces necrotic fibrin tissue and scar formation, chronic inflammation and the necessity of antibiotic treatments.

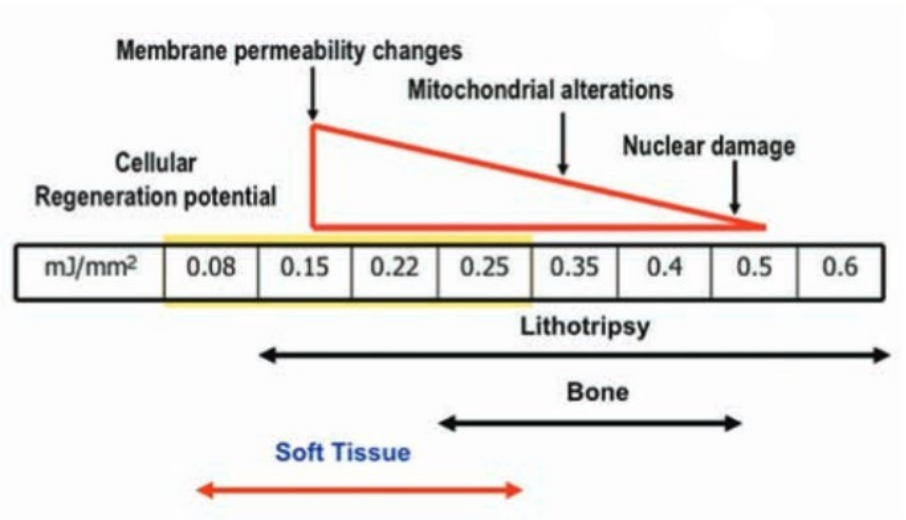
Since shock waves are non-invasive, they represent a cost-effective alternative to conservative and surgical wound care. It is safe, with very rare complications and bears risks or severe side effects. If necesssary, it can be applied in an outpatient environment as well,

making it also accessible of patients confined to bed. One major advantage of this method is that there is no need for anesthesia, in contrast, shock waves are known to relief the burden of pain. The treatment is technically easy to perform and convenient to apply for its user.
If conservative treatment fails, surgery does not have to be neccessarily be the only choice since shock wave therapy represents a real, non-invasive, cost-effective treatment alternative [87].

## 4.3. Efficacy of shock wave therapy

Importantly, shock waves applied to wounds differ considerably from those used in lithotripsy and from those used in orthopedic applications in terms of focus, frequency of applied shockwaves, energy flux density, and total number of impulses. Shock waves used in treating problematic wounds were not determined to be destructive, rather they have been shown to induce/normalize biological responses, which stimulate and support tissue repair and regeneration [16]. For example, an interesting study has been performed by Zhang *et al.* where they investigated the dose-effect relationship of SWT *in vitro* [44]. They divided endothelial progenitor cells into different treatment groups regarding energy densities and shock number and examined the expression of angiogenic, apoptotic and inflammation factors. After proving the dose-effect relationship in SWT, they suggest a shock intensity ranging from 0.10-0.13 mJ/mm(2) and shock number ranging from 200-300 impulses to be the optimal parameters for ESWT to treat cells in vitro [44].

**Schematic representation of the enregy spectrum of ESWT and its clinical use**
(Scheme taken from: [47])



# 5. Summary and conclusions

## 5.1. Metaanalysis and review assessments

So far, summarizing the research and clinical evidence which shows considerable success of shock wave therapy in wound healing we can conclude that it represents a promising and beneficial (adjuvant) treatment option for patients suffering from severe skin injuries. Antonic *et al.* sum up that current literature supports this treatment modality due to its efficacy, reproducibility, and virtually no adverse effects. Negative effects of chronic inflammation are suppressed after the treatment leading to improved wound healing, improved tissue perfusion, and increased blood vessel formation. Difficult to heal and chronic wounds show significant improvement after the treatment with a low rate of wound recurrence. Treatment is clinically effective, non-invasive (no morbidities related to surgery), is well tolerated by patients, does not require anesthesia, and is cost-effective and easy to apply on an outpatient basis. [47] In their systematic review, Dymarek *et al.* deduce the effectiveness by analyzing randomized, controlled clinical trials, non-randomized studies as well as non-controlled studies. They conclude that substantial clinical evidence confirms ESWT utility and the range of positive results, such as completed wound closure and reepithelialization, enhanced tissue granulation, reduced necrotic fibrin tissue, improved blood flow perfusion and angiogenesis, reduced period of total wound treatment, and decreased necessity of antibiotic treatment. [75] Given the high burden of the healthcare system by the costs associated to the management of acute and chronic wounds, accelerated healing and the reduction of the treatment period by adjunctive shock wave therapy will be highly beneficial for the individual patient and the public health.

## 5.2. Outlook / future prospects

Discovering the mechanism of mechanotransduction induced by shock waves forces are currently under intensive investigation and potential targets have already been identified and further research of this promising technology is imperative. [47]

Nevertheless, additional well-designed clinical studies and meta-analyses are necessary to investigate ESWT safety, efficacy, and cost-effectiveness in patients suffering from wide range of skin wounds. Sham-controlled, randomized, multicenter, blinded clinical trials with the highest methodological quality and scientific data reliability are needed to ascertain ESWT efficacy and develop explicit evidence-based guidelines and recommendations. [75] In the future, ESWT may play an important role in wound care where evidence-based practical guidelines and defined therapy protocols for different types of wounds should be developed.

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