



Shock Wave Therapy for Wound Healing and Scar Treatment

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Background

To influence the evolution of an excessive scar toward a normal scar, several physical treatments exist to manage hypertrophic scarring. Physical treatments include manual and mechanical massage, physiotherapy, thermal therapy, and shock wave therapy. Manual massage has a wide array of beneficial effects on scars such as drainage of edema, reduction of pain, and pruritus and hydration of the skin [1]. Mechanical massage or vacuum massage uses gentle vacuum suction to lift the skin and to create a skin fold [2]. Since scars have a propensity to retract and create contractures in joints, splinting, taping, and posture stretching play a crucial role in the treatment. Thermal therapy includes high pressure showers, thread-like showers, and high pressure water and aims to mobilize the skin, to improve flexibility and to reduce inflammation, pain, and pruritus. All of these techniques are frequently used; however, there is only little supporting evidence [3].

The ideal non-invasive scar treatment should be safe, well tolerated by patients, have low associated complication rates, is easy to apply, cost-effective, and can be used in an outpatient setting. Shock Wave Therapy (SWT) meets all the aforementioned requirements [4–7]. The application of shock wave therapy in scar management (■ Fig. 55.1) is still in its exploration phase; however, there are some interesting findings [3].



■ Fig. 55.1 Shock wave application on a scar

55.1 Working Mechanism of SWT in Relation to Skin Defects

SWT converts external mechanical stimuli into biochemical cell reactions (e.g., gene transcription leading to collagen remodeling) in living tissue, supported by mechanotransduction pathways, which result in the activation of numerous cellular events, responsible for the positive effects of SWT on cell metabolism and cell

cycle [8]. Moreover, as in some other mechanotherapies applied in clinical practice, the main action of SWT seems to focus on inducing tissue regeneration and matrix remodeling *in vivo* [9]. Fibroblasts are the major mechanoresponsive cells in connective tissue, and are therefore the main target of SWT [10, 11]. Fibroblasts play a crucial role in remodeling of the extracellular matrix (ECM) by synthesizing and organizing connective tissue components, and there is a strong believe that SWT has a modulating effect on these actions and could therefore be of interest in scar prevention and management.

Sukubo et al. (2015) described the beneficial effects of SWT on macrophage behavior. SWT does not activate resting macrophages and seems to modulate macrophage activity in the inflammatory phase of wound healing. It inhibits the M1 (pro-inflammatory) activation in the initial inflammatory phase and enhances the M2 (anti-inflammatory) activation in the late inflammatory phase [12]. SWT can also regulate inflammation via TLR3 pathway in three phases. In an initiation phase, it induces a pro-inflammatory reaction mediated by cyclophilin A and IL6. There is a suppression of inflammation in the middle phase and in the limitation phase, there is a late anti-inflammatory effect mediated by IL10 [13]. Both findings indicate that SWT, applied in the wound healing stage or in the early stage of scar development, could prevent pathological scarring.

Non-randomized clinical data suggest that SWT is beneficial in terms of improved skin elasticity and revitalizing dermis in females with cellulite [14]. Fibrillar adipose tissue fibrosis looks very similar to dermal scarring [15], so the outcomes of clinical trials investigating cellulite could be transferred to pathological scarring [2]. MR imaging has shown that fibrous septa, visualized in 97% of the area with cellulite depressions, are markedly thickened in cellulite afflicted areas. Shockwave energy might weaken the fibrous septa, and thus the afflicted skin becomes smoother [14]. There is evolving experimental data suggesting SWT activation pathways in adipose-derived stem cells [14].

Delayed wound healing might be considered as one of the main reasons to develop hypertrophic scars. SWT has repeatedly proven to be effective as a wound-healing modality by decreasing time to full wound closure [4, 5, 16, 17]. From the mechanobiologic point of view, it has been described that the neoangiogenic capacity could be related to the inhibition of endothelial cell apoptosis, occurring in the very early phase after SWT stimulation (first 3 hours), as an initial response to the mechanical stimulus. More in detail, it seems possible to detect some “preparatory” signals, such as downregulation of the genes involved in cell cycle, adhesion and apoptosis, probably correlated to an upcoming detachment of endothelial junction [9]. After a low-energy SWT treat-

ment (800 shocks, 1 Hz, 0.03 mJ/mm²), mRNA expression and protein levels of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) were significantly upregulated. Furthermore, the SW therapy enhanced phosphorylation of caveolin-1 and the expression of HUTS-4 that represents β 1-integrin activity. These results suggest that caveolin-1 and β 1-integrin are involved in the SW-induced activation of angiogenic signaling pathways [18].

We can summarize that the overall effect of SWT is an improvement of tissue homeostasis, accompanied by an improvement of the tissue self-healing abilities.

55.2 SWT Dose Effect Relationship

For a full treatment outline, the energy flux density (EFD), the number of pulses, the pulse frequency, and the number and interval of treatments are the most relevant parameters [5]. Differences in these parameters can lead to varying outcomes, emphasizing the dose dependency of these mechanotransduction events [9]. High-energy SWT can suppress cell growth, while low-energy shock waves might enhance cell proliferation [19]. SWT applied with an EFD of 0.01–0.03 mJ/mm² can modulate the inflammatory pathway in which macrophages are involved [12], and with an EFD of 0.08 mJ/mm² SWT can regulate inflammation via the TLR3 pathway. The EFD for soft tissue indications is typically in the range of 0.08–0.25 mJ/mm² [4], while scars and fibrosis are treated with an EFD ranging between 0.15 and 0.33 mJ/mm². SWT settings of 0.22 mJ/mm² and 1000 pulses seem to be ideal for fibroblast viability and growth [20]. Fibroblast viability was also influenced by the number of pulses. The higher the number, the more risk for cell destruction [11]. Each cell type seems to be responsive to SWT but probably with different optimal device settings and ranges of mechanical stimulation, thus developing different biochemical effects [8]. A study by Lee et al. showed that the EFD plays an important role in the targeting of specific mechano-signaling pathways, with 0.12 mJ/mm² being the optimal dose for activating the mTOR-FAK pathway [21] and 0.10 mJ/mm² showed the best results for inhibiting TGF- β 1/Smad pathway [22] (■ Table 55.1).

55.3 The Effects of Shock Wave Therapy in Soft Tissue Defects

55.3.1 The Effects of SWT in Wound Healing

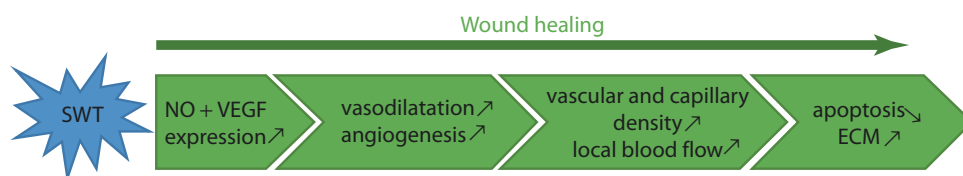
Wound healing after SWT is characterized by an upregulation of the angio-active factors such as nitric oxide (NO) and vascular endothelial growth factor (VEGF) leading to induced angiogenesis [17], vasodilatation, increase in vascular and capillary density, and increased local blood flow. NO and VEGF are extremely important, both in early stage and late stage healing [5, 7, 9, 11, 17]. It has been suggested that an aspect of the early gene response of endothelial cells to SWT is characterized by a decreased apoptosis and stimulation of the extracellular matrix metabolism [5, 9]. SWT will lead to reduced tissue necrosis in wound healing by increasing cellular proliferation and procollagen production [11, 23]. In terms of timing, vasodilatation is noticed at an early stage (first 3 days) and neovascularization at late-stage post intervention [17]. In a clinical trial investigating the efficacy of ESWT to heal chronic therapy-refractory ulcers, the underlying molecular mechanisms were also studied *in vitro* [24]. Fibroblasts reorganized in a radial and star-shaped clustered manner and had large “stress” fibers. Cluster formation of fibroblasts was dose dependent, meaning that more applications lead to higher clustering. Shock waves also induce upregulation of 67 genes for keratinocytes and 652 genes for fibroblasts, suggesting that SWT mainly targets fibroblasts [24]. The upregulation of Vimentin on mRNA level leading to a visible reorganization of the cytoskeleton provided yet another proof for mechanotransduction as working mechanism for this intervention.

Besides “general wound healing,” SWT has specifically been proven effective in burns. First, SWT applied upon donor site healing burn wounds shows a significantly shorter time to complete epithelialization [25]. Second, burn area perfusion has been evaluated with Laser Doppler Imaging before and after SWT and showed a significantly increased perfusion after extracorporeal shockwave therapy treatment [26]. The review of Antonic et al. suggested that SWT may decrease the need for surgical intervention and associated morbidities in patients with severely deep partial- or full-thickness

■ Table 55.1 Suggested SWT settings for electro-hydraulic devices when treating wounds or scars

	Energy flux density	Number of pulses	Pulse frequency	Treatment interval	Number of treatments
SWT for wound healing	0.03–0.20 mJ/mm ²	500–1000	4–6 Hz	1× per week	1–3
SWT for scar treatment	0.15–0.33 mJ/mm ²	800–1500	4–6 Hz	1× per week	8–12

Fig. 55.2 Cascade of wound-healing processes after SWT



burns [4]. Joo et al. demonstrated that ESWT significantly reduced burn scar pruritus severity and activities-of-daily-living disturbances compared to a control group who received sham treatment. The EFD ranged between 0.05 and 0.20 mJ/mm², which seemed useful for pruritus in burn scars [27]. The authors hypothesized that ESWT targeted “neurogenic inflammation,” which is an inflammation caused by the release of substances (e.g., SP and CGRP) from primary sensory nerve endings. Nerve fiber loss and the depletion of neuropeptides might decrease inflammation, and thus may decrease itch [28]. A recent meta-analysis showed that ESWT had better therapeutic outcomes on acute and chronic soft tissue wounds when compared to Conventional Wound Therapy (CWT) [29]. The meta-analysis showed that ESWT statistically significantly increased the healing rate of acute and chronic soft tissue wounds 2.73-fold (odds ratio, OR = 3.73, 95% confidence interval, CI: 2.30–6.04, $P < 0.001$) and improved wound-healing area percentage by 30.45% (Standardized Mean Difference (SMD) = 30.45; 95% CI: 23.79–37.12; $P < 0.001$). ESWT reduced wound-healing time by 3 days (SMD = –2.86, 95% CI: –3.78 to –1.95, $P < 0.001$) for acute soft tissue wounds and 19 days (SMD = –19.11, 95% CI: –23.74 to –14.47, $P < 0.001$) for chronic soft tissue wounds and the risk of wound infection by 53% (OR = 0.47, 95% CI: 0.24–0.92, $P = 0.03$) when compared to CWT alone. Serious adverse effects were not reported [29] (■ Fig. 55.2).

55.3.2 The Effects of SWT in Scar Management

Fibrous tissue can be reduced by SWT (at the origin) during wound healing processes, but it can also be remodeled in a second phase of scar formation. Primary data show that height, pliability, vascularity, and pigmentation, all relevant scar parameters, show improvement after SWT [6, 30]. The change in these physical and physiological parameters will probably lead to amelioration in function, which is, for example, demonstrated by an increase of passive ROM reported in a study on retracting hand scars [30]. Subjective pain measures also show a decrease in pain at the scar site after SWT [6, 30].

On a histopathological level, the effects of SWT on fibrosis are plural. A downregulation of alpha-SMA expression, myofibroblast phenotype, TGF- β 1

expression, fibronectin, and collagen type I are measured. A significant increase in dermal fibroblast-like phenotype with low contractility and high migratory ability, small vessel density and precursors of extracellular matrix components, probably leads to new and thinner collagen fascicles and parallel orientation to the dermo-epidermal junction [30–32]. Synergistic alterations in pro- and anti-fibrotic proteins (TGF- β 1 and MMP-2, respectively) suggest a reduced capsule formation after silicone implantation [33]. One study compared ESWT to triamcinolone injections for the treatment of keloids. ESWT showed comparable functional outcome, together with comparable total sum of scores for POSAS patient scale and POSAS observer scale clinically. A significant reduction in collagen fibers and increased expression of MMP-13 degrading enzyme could be seen when compared to intralesional steroid injection [34]. Zhao et al. demonstrated positive results on planimetric scar characteristics and inhibition of TGF- β 1/Smad signaling pathway with Radial Extracorporeal Shockwave Therapy [22], as well as decreased Scar Elevation Index, fibroblast density, and α -smooth-muscle-actin expression in hypertrophic scar tissues of a rabbit model [35].

The most promising results in the research for the effects of SWT on scars were presented as preliminary data of an ongoing randomized placebo controlled trial investigating the effects of SWT in the management of hypertrophic scars. The results of the objective assessments showed a statistically significant better performance of the intervention group for elasticity assessed with cutometry [36] (■ Table 55.2).

55.4 Conclusion

All the presented findings are fundamental knowledge for further investigation of SWT to reduce the fibrous component in regenerating and remodeling tissues. The dose dependency of the treatment effects remains understudied. Energy Flux Density, number of shocks, shock frequency, and treatment interval and number are all important parameters in the choice for the most suitable device settings, in relation to the indication. Future studies should include these parameters as covariates to determine the right-specific approach for each scar. The full potential of SWT in wound healing, scar treatment, and cellulite certainly needs further unraveling.

Table 55.2 SWT effects on wound healing, scar formation + remodeling, and cellulite

Effect of SWT on	Changes in histopathological parameters	Physical and physiological changes
Wound healing	Stimulation of the ECM metabolism Upregulation of cell-cycle regulatory genes Reorganization of the cytoskeleton	Angiogenesis Vasodilatation Increase in vascular and capillary density Increase in local blood flow Decrease in apoptosis Reduction of tissue necrosis
Burn wound healing		Shorter epithelialization time Increase in perfusion
Scar formation and remodeling	Downregulation on alpha-SMA expression, myofibroblast phenotype, TGF- β 1 expression, and fibronectin Decrease in collagen type I Upregulation dermal fibroblast-like phenotype Increase small vessel density (ratio type I/type III collagen) Increase in precursors of ECM components Synergistic alterations in pro- and anti-fibrotic proteins	Formation of new and thinner collagen fascicles Reduced capsule formation Decrease in height Increased pliability Normalization of vascularity and pigmentation Amelioration of function (range of motion) Decrease in pain
Cellulite	Decrease of serum malondialdehyde and plasma protein carbonyls Release of lipid peroxidation products influence adipose-derived stem cells	Weakening of the fibrous septae Smoothering of skin

Take-Home Messages

- SWT meets all the requirements for the ideal non-invasive scar treatment.
- Mechanotransduction is the working mechanism behind SWT.
- SWT induces tissue regeneration and remodeling *in vivo*.
- Inflammation can be modulated by SWT.
- Low-energy SWT induces cell proliferation, while high-energy SWT suppresses cell growth.
- SWT can decrease time to full wound closure and reduces the risk for tissue necrosis.
- SWT may improve scar elasticity, which will probably lead to amelioration of function.
- There is a high dose–effect relationship when treating soft tissue defects with SWT.

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