MTS Science White Paper©

SoftWave™- Pain Therapy

Research Assessment & Scientific Guide

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CONTENT

SPARK OF LIFE

1. Rationale

An increased occurrence of pain has drastic and costly effects on the worldwide population in terms of their performance at work and daily quality of life, specifically, when moderate to severe chronic pain occurs and patients receive inadequate treatment. Many painkillers have strong side effects and are addictive. In addition, the development of tolerances leads to the use of increasingly higher doses. It is time for a global change of course in the current management of chronic pain.

For many decades, regenerative extracorporeal shock wave therapy (ESWT) has been used effectively for the treatment of acute and chronic pain in a variety of pain syndromes; For example: chronic pelvic pain, lower back pain / sacroiliac joint pain, shoulder pain, trochanteric pain, angina pectoris, intermittend claudication, etc. Whenever conservative therapy has not been effective in relieving pain and other symptoms, non-invasive ESWT has been used, yielding results of pain relief and improved function.

The precise underlying mechanism, how ESWT intervenes in the vicious cycle of (chronic) pain, is not yet fully understood. This paper describes existing hypotheses and provides the link between biological cause and medical effect of this therapy in the resolution of pain, based on the latest scientific knowledge and current findings.

2. Introduction and Definitions

2.1. The Basic Principles of SoftWave™ Therapy

SoftWaves are high-energy acoustic waves that behave much like other sound waves, except that they have much greater pressure and energy. The energy of a shock wave is released as pressure on the environment. This pressure wave builds up extremely quickly and consists of a very high positive and a minor negative part.

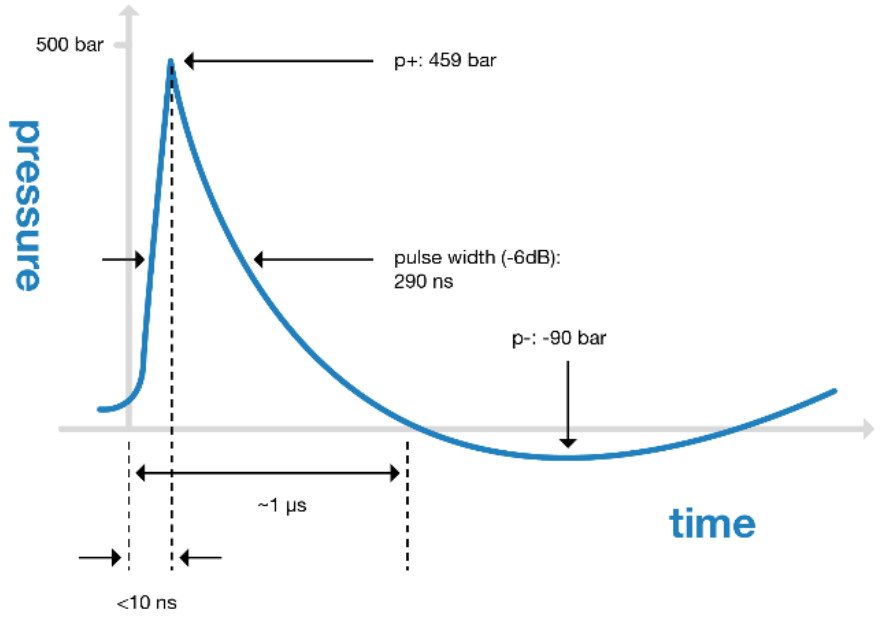

Figure 1. Schematic Pressure Profile of a Focused Shock Wave. Characteristic poperties: Extremely fast rise of the curve, very high pressure, low negative wave compared to very high peak pressure.

The original principle used in medicine is that, in which, the shock waves are generated by a spark plug, the electrohydraulic principle. The technology that generates the shock wave has a considerable influence on the energy distribution. SoftWave technology uses traditional electrohydraulic generation principles

and ensures optimum energy composition and distribution; the pressure amplitude is mainly positive with only minimal negative tensile wave energy and provides regenerative energy not only in the focal area, but in the entire acoustic field extending from the spark source.

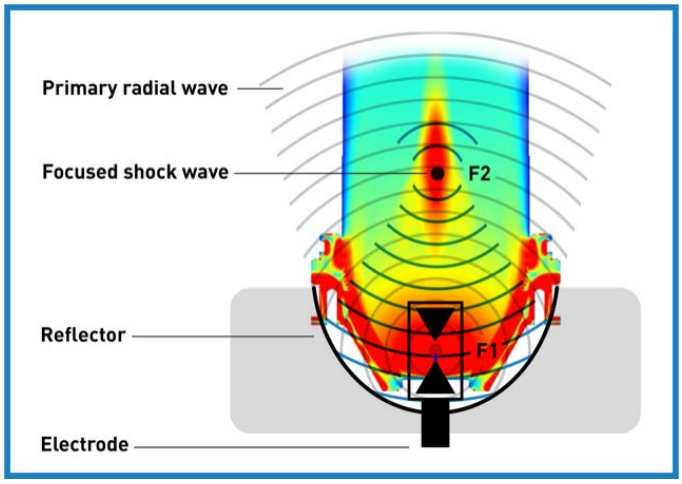

Figure 2. Eletrohydraulic Shock Wave Generation. An electrode is placed in the first focal point of a water-filled semi-ellipsoid reflector and high voltage is applied to the tips of the electrode. Thereby, an electric spark is generated between these tips and a spherical shock wave is released by the rapid vaporization of the water between the tips. The shock wave spreads out from the applicator leading to a low intensity radial primary wave, followed by a focused shockwave with focus F2 which occurs due to the reflection of the spherical wave at the reflector. The colours display imaging by a DICOM (Digital Imaging and Communications in Medicine) MATLAB (matrix laboratory) simulation of the acoustic field with SoftWave technology. Red corresponds to the area with the maximum energy.

In regenerative medicine, the physical energy of SoftWaves is applied to all kinds of tissues at a desired depth and with an adjustable energy flux density (EFD), depending on the respective indication and pathophysiology. With its unique wide focus size, SoftWave Technology delivers the highest possible amount of total biologically effective energy to the target area. This physical energy -as a biological response- produces mechanical stimulation which is recognized by mechanoreceptors of the cell and transduced into to various cellular responses: The expression and release of regeneration-associated molecules, like growth factors and other signaling molecules (chemokines and cytokines), is activated. All these factors trigger intracellular signalling cascades which are implicated in processes like metabolic activation, proliferation, migration and recruiment of mesenchymal and haematopoetic progenitor cells. This action leads to reduction of inflammatory processes, as well as to improve angiogenesis and neovascularisation, resulting in tissue remodelling and regeneration.

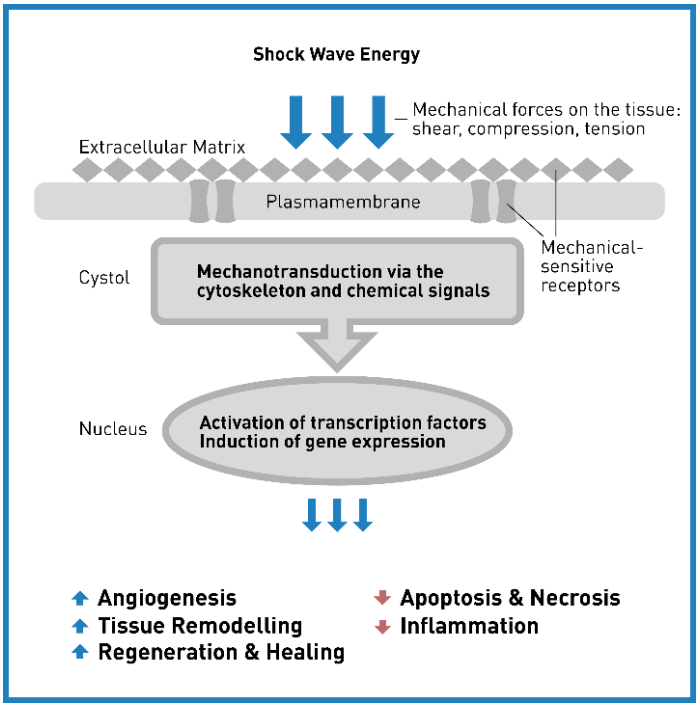

Figure 3. Mechanotransduction Mechanism - Phases of SoftWave Therapy.
1. Physical Phase: Shock waves generate a positive pressure to generate absorption, reflection, scattering and transmission**. 2. Chemical Phase:** The mechanical stimulus leads to biochemical reaction, biomolecules are released and cell signaling pathways are activated. **3. Biological Phase:** Modulation of angiogenesis, alteration of inflammatory response, bone and soft tissue healing.

2.2. The Basic Science of Pain

Pain

As a submodality of somatic sensation, has been defined as a "*complex constellation of unpleasant sensory, emotional and cognitive experiences provoked by real or perceived tissue damage and manifested by certain autonomic, psychological, and behavioral reactions*". [1]

Nociceptors

Peripherally localized excitatory neurons preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged. Two distinct populations of afferent axons conduct impulses caused by pain, inflammation or tissue damage. The first group -the myelinated A delta and beta fibers- conduct cold and well-localized pain sensations. The second group -the unmyelinated C fibers- signal pain that is poorly localized or caused by heat or mechanical stimuli (according to the Erlanger-Gasser Classification of sensory fiber types). They release glutamate as their primary neurotransmitter as well as other algesic components such as the following: prostaglandins, Substance P, calcitonin gene-related peptide (CGRP), bradykinin, and somatostatin or histamine which are important in both central synaptic signaling and efferent signaling in the skin. The fibres of nociceprtors synapse in the dorsal horn of the spinal cord where spinal modulation occurs. [2]

Acute Pain

Acute (transient) high intensity stimuli yield a somatotopically limited pain sensation that resolves upon the removal of the stimuli. The encoding of the stimulus involves specific activation of subpopulations of nociceptors which are endowed with their response property by virtue of specific channels expressed on their terminals. The speed of transmission is directly correlated to the diameter of axons of sensory neurons, and whether or not they are myelinated. Most nociceptors have small diameter unmyelinated axons (C-fibers) bundled in fascicles, surrounded by Schwann cells, and support conduction velocities of 0.4–1.4 m/s). Initial fast-onset pain is mediated by A-fiber nociceptors (β and δ), whose axons are myelinated and support conduction velocities of approximately 5–30 m/s (most in the slower Aδ range). This acute afferent traffic leads to activation of supraspinally projecting dorsal horn neurons; The frequency of their activation being dependent upon the frequency of afferent input and accordingly stimulus intensity. [3]

Tissue injury

Tissue injury arising from ongoing exposure to high-intensity stimuli leads to a pain sensation continuing beyond the removal of the originating stimulus. There is, in addition, an enhanced sensitivity to otherwise modestly aversive stimuli applied to the injured tissue (hyperalgesia). Typically, such pain resolves in parallel with resolution of the injury state (healing). At the peripheral terminal, injury pain or inflammation leads to an innate immune cascade yielding release of active factors from blood, local and migrating inflammatory cells, and injured cells. These products (pro-excitatory neurohormones like cytokines or chemokines) initiate activity in C fibers, through receptors, located on the afferent terminal and sensitize these terminals. At the level of the spinal dorsal horn, ongoing afferent traffic leads to initiation of a robust facilitation of dorsal horn output. [3]

Development of Neuropathic / Chronic Pain

Acute pain is a warning mechanism that exists to prevent tissue damage; however, pain can outlast its protective purpose and persist beyond injury, becoming chronic. Chronic pain is maladaptive and needs addressing, as available medicines are only partially effective and cause severe side effects. Dramatic changes occur in both peripheral and central pathways resulting in an altered perception of pain characterized by Hyperalgesia, Allodynia and spontanous firing of nociceptors due to nerve damage. [4]

Petripheral nerve damage
Leads to a pain state with persistency and components of – 1. Hyperalgesia, the phenomenon where there is an enhanced sensation of pain at normal threshold stimulation. The pathophysiology is believed to arise from the sensitisation of nerves in and around the damaged area due to the release of signalling peptides and – 2. Allodynia, where pain is felt on a (non-noxious) stimulus which was previously not painful. Allodynia is also observed in and around areas affected by noxious stimuli.
The peripheral and spinal mechanisms underlying this increased spontaneous nociceptor activity in tissue or peripheral nerve injury are (amongst others):

- Altered channel expression that are critical in controlling the neurotransmitter release
- Loss of inhibitory hyperpolarization of dorsal horn nociceptive neurons
- Activation and migration of non-neuronal inflammatory cells (microglia and astrocytes/T-Cells and macrphages)
- Altered expression of pro-excitatory cytokines such as the following: TNFα, bradykinin, NGF, interleukins, and catecholamines and their receptors [3]

Inflammatory pain
Pain associated with tissue injury and inflammation characterized by reduced threshold and increased responsiveness.

Neurogenic inflammation
A general term used to describe the effects of the local release of inflammatory mediators such as substance P and CGRP from afferent nerve terminals.

Cytokines
Small secreted proteins released by cells that have a specific effect on the interactions and communications between cells. Cytokine is a general name; Other names include the following: lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). There are both pro-inflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation, but also the persistence of pathologic pain by directly activating nociceptive sensory neurons. Certain inflammatory cytokines are also involved in nerve-injury / inflammation-induced central sensitization, and are related to the development of contralateral hyperalgesia / allodynia. [5]

2.3. The Interface Between the Immune and Nervous Systems – Key Factors in the Pathophysiology of Pain

Peripheral nerve injuries and diseases often lead to pain persisting beyond the resolution of damage, indicating an active disease-promoting process, which may result in chronic pain. This is regarded as a maladaptive mechanism resulting from neuroinflammation, that originally serves to promote regeneration and healing. Knowledge on these physiological and pathophysiological processes has accumulated over the last few decades, and has started to yield potential therapeutic targets; Key players are macrophages, T-lymphocytes, cytokines, and chemokines. In the spinal cord and brain, microglia and astrocytes are involved. Both proinflammatory and anti-inflammatory cytokines show an important role in neuropathic and other chronic pain states in humans. MicroRNAs and other noncoding RNAs have been discussed, as potential master switches, that may link nerve injury, pain, and inflammation. [6]

Immune cells and glia interact with neurons to alter pain sensitivity and to mediate the transition from acute to chronic pain. In response to injury, resident immune cells are activated and bloodborne immune cells are recruited to the site of injury. Immune cells not only contribute to immune protection, but also initiate the sensitization of peripheral nociceptors. Through the synthesis and release of inflammatory mediators and interactions with neurotransmitters and their receptors, the immune cells, glia, and neurons form an integrated network that coordinates immune responses and modulates the excitability of pain pathways. The immune system is also able to reduce sensitization by producing immune-derived analgesic and anti-inflammatory or proresolution agents.

Macrophages, leukocytes, mast cells, glial cells, and T lymphocytes are immune cells involved in the peripheral and central pain pathways. In response to tissue damage and nerve injury, these cells are activated and release inflammatory mediators and cytokines in the skin, peripheral nerves, dorsal root ganglia, and spinal cord. A variety of factors are released upon tissue damage which lead to the activation of nociceptors. Neurotransmitter, neuromodulators, and inflammatory mediators are released from primary afferent terminals into the spinal cord. Many of these factors are pro-inflammatory and lead to acute inflammation in the area of damage. Cytokines, tumour necrosis factor (TNF), interleukins (IL-1b, IL-6)), adenosine triphosphate (ATP), substance P, CGRP, monocyte chemotatctoc protein-1 (MCP-1/CCL2), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) are released by activated immune and glial cells (Schwann cells, microglia, satellite cells, and astrocytes). These immunological responses and the infiltration of immune cells into the CNS are involved in the pathogenesis of neuropathic and chronic pain. [7,8]

Proinflammatory Cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is abundant evidence that certain pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α are involved in the process of pathological pain. Among the many immune- or glia-derived mediators that are related to pain hypersensitivity, IL-1β is a key cytokine that modulates microglia, astrocytes and neurons. IL-1β was found to increase the production of substance P and prostaglandin E_2 (PGE_2) in a number of neuronal and glial cells. IL-6 has been shown to act as a messenger in conveying peripheral immune signals to the CNS and to contribute to neuropathic pain following a peripheral nerve injury. Blood levels become increased after inflammation. The increase in circulating IL-6 is associated with induction of cyclooxygenase-2 (COX-2) activity and Prostaglandin E_2 (PGE2) release in vascular endothelial cells of the brain. Neutralization of IL-6 attenuates inflammatory hyperalgesia. TNF-α is upregulated in pain pathways after injury and secreted by immune and glial cells. [5]

TNF-α (Tumor Necrose Factor Alpha) is a key inflammatory cytokine that plays a key pro-nociceptive role. It is released by stimulated macrophages, upon nerve injury, and induces peripheral nociceptor sensitization. TNF-α has been shown to play important roles in both inflammatory and neuropathic hyperalgesia and allodynia. Injection of TNFα into sciatic nerve elicits hyperalgesia and allodynia that last for days, which is associated with nerve edema, Schwann cell injury, and macrophage activation. It was shown that topically applied TNFα induced ectopic firing in C and A-delta fibers. Local TNFα also lowered the mechanical threshold of C-nociceptors and caused ongoing activity in some C nociceptors. The level of TNFα in DRG is increased after peripheral nerve injury, as well as, the two TNFα receptors, TNFR1, and TNFR2. TNFα blockade prevented or relieved neuropathic pain. [5]

Anti-Inflammatory Cytokines are a series of immunoregulatory molecules that control the pro-inflammatory cytokine response. Major anti-inflammatory cytokines include interleukin (IL)-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13. Leukemia inhibitory factor, interferon-alpha, IL-6, and transforming growth factor (TGF)-β are categorized as either anti-inflammatory or proinflammatory

cytokines, under various circumstances. Specific cytokine receptors for IL-1, TNF-α, and IL-18 also function as inhibitors for pro-inflammatory cytokines. Among all the anti-inflammatory cytokines, IL-10 is a cytokine with potent anti-inflammatory properties, repressing the expression of inflammatory cytokines, such as, TNF-α, IL-6, and IL-1 by activated macrophages. In addition, IL-10 can up-regulate endogenous anti-cytokines and down-regulate pro-inflammatory cytokine receptors. [5]

Substance P's most well-known function is as a neurotransmitter and a modulator of pain perception, by altering cellular signaling pathways. Substance P is also a key molecule in the neurogenic inflammation response, a critical interaction between the nervous system and the immune system. Additionally, the function of substance P is involved in the pathogenesis of various diseases, including but not limited to the following: cancer, diabetes, rheumatoid arthritis, myocarditis, heart failure, epilepsy, migraine, thrombosis, pruritus, depression, and anxiety. [9]

CGRP (Calcitonin Gene-Related Peptide) is a member of the calcitonin family of peptides. It is widely distributed in nociceptive patways in both the peripheral and the central nervous systems. Furthermore, it is a potent vasodilator. When synthesized in the dorsal horn of the spinal cord, CGRP is linked to the transmission of pain. The current literature suggests that CGRP may play a role in nociception of somatic pain conditions and proinflammatory role in chronic pain. [10]

NO (Nitric Oxide) is involved in many physiological processes and several lines of evidence have indicated that NO plays a complex and diverse role in the modulation of pain. Nitric oxide is an important neurotransmitter involved in the nociceptive process and, in the dorsal horn of the spinal cord, it contributes to the development of central sensitization. On the other hand, experimental data have also demonstrated that NO inhibits nociception in the peripheral and also in the central nervous system. In addition, it has been shown that nitric oxide mediates the analgesic effect of opioids and other analgesic substances. [11]

BNDF (Brain-derived Neurotrophic Fator) is a crucial neuromodulator in pain transmission, both in peripheral and central nervous system (CNS). Despite evidence of a pro-nociceptive role of BDNF, recent studies have reported contrasting results, including anti-nociceptive and anti-inflammatory activities. [12]

TLRs (Toll-Like Receptors) are transmembrane protein receptors present in dendritic cells, macrophages, and glial cells. TLRs found on the Schwann cells surrounding the C fibres of primary sensory neurons have an important role in opioid tolerance and in the initiation of both inflammation and neuropathic pain. Of the 10 subtypes of TLRs in humans, the TLR2, TLR3 and TLR4 subtypes are crucial for glial activation and response in neuropathic and chronic pain mechanisms. TLR activation releases pro-inflammatory mediators such as MCP-1, ROS, NO, IL-6, IL-1a, TNF, IL-5, IL-3, IFN b, CXCL10, CCL5, inducible NO synthase, PGE2 and calcitonin gene-related peptide [7]

3. Pain Pathways Modulated by Shock Wave Therapy

SWT efficiently relieves acute and long-lasting chronic pain in a multiple of indications. The question remains, which basic biomolecular mechanisms and signalling pathways modulated by SWT are responsible for this effect? Based on research and clinical evidence, different aspects and multifactorial correlations are considered to be responsible for the analgesic effect of shock wave therapy.

3.1. Nociceptive Hyperstimulation / Gate-Control Theory

The expected mechanism is based on the interruption of high-frequent nerve impulses of peripheral nociceptors, by the intense mechanical pressure of shock wave, in the treated tissue (hyperstimulation analgesia). These intense stimulations are transmitted to the central nervous system, through the posterior column of the spinal cord, and are supposed to activate the descending inhibitory system that block a subsequent transmission of nociceptive stimuli, according to the *gate-control theory*. [13] The *gate-control theory,* proposed by Melzack and Wall, states that the neural signals in the dorsal horn from the peripheral input will increase or decrease the flow of impulses to higher processing centers in the central nervous system. [2] This means that in a standard nociceptive system, for instance, the amount of pain generated by a primary nociceptive stimulus, will be reduced during and after the presentation of a second nociceptive stimulus. This is due to the activation of endogenous analgesia, i. e., the release of endorphins and other analgesic molecules. Since the analgesic effects of SWs are more prominent when the maximum energy density tolerable by the patient is applied, it is therefore reasonable to accredit analgesia to the activation of the descending inhibitory system. [14]
It is also assumed that shock waves change the nature of the cell membranes, and thus, no action potential can be built up, consequently pain perception is reduced. Furthermore, shock waves change the chemical environment of the cell membranes by generating free radicals, which in turn result in pain-inhibiting chemicals in the vicinity of the cells. [15–19]

3.2. Associative Pain Memory Theory

Another theory introduced by Dr. O. Wess, in 2008, was the associative model for establishing reflex functions, the formation of a pain memory. Chronic pain, for example, without underlying anatomical disorders is considered a pathological control function. An interaction between afferent sensor input and efferent motor output is postulated to form a reflex-like response. The hypothesis behind is a “malfunction” of the nervous control system due to “pathologic reflexes,” which may be conditioned by single overuse or long-term misuse of particular organs or functions. Accordingly, a *circulus vitiosus* of pain sensation and muscle and / or vessel contraction is generated when pain becomes chronic. Pathological adaptation to unnatural muscular and vascular tone conditions is assumed to take place, within the nervous system, on the synaptic level by modification of the synaptic strength of large ensembles of neurons. Adaptation of synaptic threshold patterns is deemed to be the basis of memory functions in general. Consequently, successful treatment regimes must affect the pathological reflex bow and erase the particular memory, instead of modifying the organ itself. ESWT with strong and repeated stimulation of synaptic junctions may delete the pathologic memory reflex pattern selectively, with respect to the treated pain area. [19]
However, Dr. Wess` *associative pain memory theory* has been criticised with regard to the idea of seperating pain from pathology. [20]

3.3. Selective Degeneration and Denervation of C Fibers

Another main hypothesis is that the analgesic effect is mediated by the selective degeneration of sensory neurons, during shock wave application, which reduces the concentration of pro-inflammatory mediators and relieves chronic pain.

To confirm this hypothesis, high-energy ESWT was applied to the ventral side of the right distal femur of rabbits. The femoral and sciatic nerves were investigated at the light and electron microscopic level after 6 weeks. ESWT caused a selective, substantial loss of unmyelinated nerve fibers, within the femoral nerve

of the treated hind limb, while the sciatic nerve of the treated hind limb remained unaffected. This probably implied that a relief of chronic pain by a transient dysfunction of nerve excitability at neuromuscular junction via selective partial denervation (degeneration of acetylcholine receptor in free nerve ending) plays an important role in the effects of ESWT application on the musculoskeletal system. [14,21–23]

Earlier, a Japanese group investigated the analgesic properties of shock wave application and analyzed whether it produces morphologic changes, in cutaneous nerve fibres, in rats. In normal rat skin, the epidermis is heavily innervated by nerve fibres immunoreactive for protein gene product (PGP) 9.5 and by some fibres immunoreactive for calcitonin gene-related peptide (CGRP). There was nearly complete degeneration of epidermal nerve fibres in the shock wave-treated skin, as indicated by the loss of immunoreactivity for PGP 9.5 or CGRP. Reinnervation of the epidermis occurredtwo weeks after treatment. This data shows that relief of pain, after shock wave application, to the skin results from rapid degeneration of the intracutaneous nerve fibres. [24] This group later demonstrated that a second application of low-energy shock waves has a cumulative effect on free nerve endings and leads to a longer-lasting antinociceptive action. [25] They also showed that shock wave exposure to the footpad significantly increased the average number of neurons immunoreactive for activating transcription factor 3 (ATF3) and growth-associated phosphoprotein (GAP-43). Shockwave exposure induced injury of the sensory nerve fibers within the exposed area. They suggested that this phenomenon may be linked to the fast desensitization of the exposure area during application and that subsequent active axonal regeneration may account for the reinnervation and the amelioration of the desensitization. [14,16,26]

3.4. Altered Pain Receptor Neurotransmission

The observed analgesic effect may also be given by the stimulation of the production of endogenous endorphins (substances which play a fundamental role in decreasing pain sensitivity), and by the inhibition of some specific receptors responsible for the activation of pain. The release of bioactive substances -in particular substance P and calcitonin gene-related peptide (CGRP)- released at the level of sensory nerve endings plays an important role in the maintenance of pain and chronic inflammation. [16]

C fibers make synapses in the dorsal horn of the spinal cord They release substance P as neurotransmitter, which is a neuropeptide formed slowly at the synapse and is also slowly destroyed; therefore, after the start of pain stimulation, its concentration in the synaptic space increases for several seconds and lasts for a few minutes after the stimulation is ended; Thus explaining why slow chronic pain gradually increases in intensity with time and persists even after the cessation of the painful stimulus. CGRP is a marker of sensory neurons, typically involved with pain perception, and was isolated, along with substance P, in capsaicin sensitive axons. [16] Both act on peripherals target cells such as mast cells, immune cells, and vascular smooth muscle cells, causing inflammation. This phenomenon is called neurogenic inflammation.

Studies performed on animals suggest that ESWT may have an influence on pain transmission to the brainstem, by acting on substance P and calcitonin gene gene-related peptide (CGRP) expression in the dorsal root ganglion and on neurovascular sprouting. [14]

ESW application to rat femurs resulted in a short-term increase of substance P at 6 hours and 24 hours post treatment, but it was significantly decreased after 6 weeks. By contrast, extracorporeal shock wave application did not result in altered prostaglandin E_2 release from the periosteum from the femur. Remarkably, there was a close relationship between the time course of substance P release found here and the well-known clinical time course of initial pain occurrence and subsequent pain relief after

extracorporeal shock wave application to tendon diseases. Accordingly, substance P might be involved in the biologic action of extracorporeal shock wave application on tissue of the musculoskeletal system. [27]

A study in rats showed that application of shock waves to the skin decreases calcitonin gene-related peptide immunoreactivity in dorsal root ganglion neurons and suggests that relief of clinical pain may result from reduced CGRP expression in DRG neurons. [28]

However, data regarding the altered expression of these pain transmitting neurohormones is controversial, as some research groups were unable to demonstrate a possible influence of low-energy ESWT on the expression of the transmitters substance P and calcitonin gene-related peptide (CGRP) in the lumbar spinal cord of the rat. Same group demonstrated no changes in the expression of endogenous opioids -met-enkephalin (MRGL) and dynorphin (Dyn)- in the spinal cord after ESWT. Therefore, the authors conclude that the endogenous opioid system is not influenced by ESWT treatment, and that it is unlikely that the application of ESWT triggers the endogenous pain control system of the rat through hyperstimulation analgesia. [29]
In line with this, studies in horses and sheep failed to show differences in neuropeptide concentrations after shock wave application and substance P- and CGRP-containing nerve fibers were not disrupted. [30,31]

3.5. Alleviation of Neurogenic Inflammatory Pain

Immune cells are significantly participating in peripheral and central pain transmission. They release inflammatory mediators that stimulate nociceptors and are therefore crucial in the development of chronic/neuropathic pain. Several studies reported that low-energy ESWT stimulates a polarity shift in the macrophage phenotype from M1 to M2. [32–35] This is particularly valuable for the inflamed cellular microenvironment from a standpoint of the regenerative potential of ESWT, because the macrophage expresses two major phenotypes. These are M1 and M2 and may depend on the given chemical signal. Since M1 is usually stimulated by microbial agents, it takes on a pro-inflammatory role. Conversely, the M2 macrophage is produced by the T-helper type 2 (Th2) immune response and exhibits an anti-inflammatory property, typically characterized by an increase in the biosynthesis of interleukins IL-4, IL-5, IL-9, and IL-13. The type 2 response is known to be directly involved in regenerative processes, after injury and macrophages elicit their protective role, mainly by the promotion of angiogenesis via the release of cytokines and growth factors. The M2 macrophage has also shown stimulation of cell proliferation and repair through polyamine and collagen synthesis in addition to other tissue remodeling functions, releasing IL-10 and IL-4. The M1 type on the other hand displays microbicidal activity and inhibits cell proliferation, releasing the inflammatory IL-6 and tumor necrosis factor-a (TNFa) cytokines. [14]

Accordingly, a clinical study in 33 patients with early osteonecrosis of the femoral head confirmed the significant reduction in pain, related to relevant biomarkers which were tested in the blood; The study revealed significant increases of serum biomarkers including, angiogenesis (NO3 and VEGF), osteogenesis (BMP-2 and osteocalcin), and regeneration (IGF) within one week to one month after the application of high dosage ESWT. At the same time, significant decreases in inflammatory cytokines (TNF-αand IL-6), pain threshold (substance P and CGRP), and tissue regeneration inhibitor (DKK-1) were also noted within one week to one month after ESWT. Therefore, it appears that ESWT is associated with systemic changes in serum biomarkers for angiogenesis, osteogenesis, anti-inflammation, pain threshold, and tissue regeneration. [36]

4. Summary and Conclusions

There is a wealth of scientific evidence that SoftWave Therapy has the potential to modulate the immune response and rebalance the key players involved in acute and chronic pain (preclinical and clinical evidence see chapter 5.). This potential of SoftWave Therapy, to address multiple focal points of pain modulation, allows clinicians to effectively address peripheral, spinal, and supraspinal mechanisms of pain transmission.

SoftWave Therapy positively influences the activity of immune cells, has an anti-inflammatory potential, including the stimulation of mesenchymal stem cells and the release of factors relevant to regeneration and healing. In addition, the shock wave intervenes directly in the signal transmission of pain and has both short-term and long-term analgesic effects.

Overall, there is no common consensus on only one mechanism by which ESWT conveys its analgesic effect. Pain involves multifactorial and complex processes and the causes of pain are also individually dependent on the nature of the underlying pathology. This is exactly the advantage of SoftWave Therapy, which intervenes at various levels of pain transmission, relieving acute pain in the short term and providing long-term relief by dissolving the actual cause through regeneration and healing.

Mechanisms underlying the effcient analgesic effect of SoftWave Therapy in acute and neuropathic persistent pain include:

- **Reduced tissue inflammation and oxidative stress**
- **Increased angiogenesis, cell proliferation, and tissue repair**
- **Improved blood circulation and tissue supply**
- **Healing tissue by increased angiogenesis and revascularization → Re-establishment of afunctional vasculature protects against pain**
- **Increase of local pain inhibiting substances**
- **Release of trigger points, reduction in passive muscle tone and spasticity**
- **Modulation of neuro-immune pathways by inhibition of pro-inflammatory signalling and stimulation of anti-inflammatory signalling at the neuromimmune interface**
- **Influencing the neuroplasticity of the pain memory**
- **Altered pain-receptor neurotransmission**

SoftWave Therapy is a non-invasive method to modulate the communication between neurons and immune cells and effectively treat neuropathic pain conditions. It is an outpatient procedure of short duration and can be repeated as often as needed. The therapy has no side effects and therefore has great advantages compared to systemic exposure to drugs (e.g. analgesics), which typically leads to considerable side effects, especially when administered over a longer period.

5. Preclinical and Clinical Evidence - Abstracts

5.1. Preclinical Evidence – Signalling Pathways Involved in the Immune-Nervous-System Interface: Pain Resolution, Anti-Inflammatory and Pro-Angiogenic Action of SWT

Note: **Reference titles written in dark blue text colour were performed with TRT/MTS SoftWave™ Technology.**

Cross selection of thematically relevant publications:

- **Shock waves promote spinal cord repair via TLR3** [37]

Spinal cord injury (SCI) remains a devastating condition with poor prognosis and very limited treatment options. Affected patients are severely restricted in their daily activities. Shock wave therapy (SWT) has shown potent regenerative properties in bone fractures, wounds, and ischemic myocardium via activation of the innate immune receptor TLR3. Here, we report on the efficacy of SWT for regeneration of SCI. SWT improved motor function and decreased lesion size in WT but not Tlr3-/- mice via inhibition of neuronal degeneration and IL6-dependent recruitment and differentiation of neuronal progenitor cells. Both SWT and TLR3 stimulation enhanced neuronal sprouting and improved neuronal survival, even in human spinal cord cultures. We identified tlr3 as crucial enhancer of spinal cord regeneration in zebrafish. Our findings indicate that TLR3 signaling is involved in neuroprotection and spinal cord repair and suggest that TLR3 stimulation via SWT could become a potent regenerative treatment option.

- **Motor and sensory Schwann cell phenotype commitment is diminished by extracorporeal shockwave treatment in vitro** [38]

The gold standard for peripheral nerve regeneration uses a sensory autograft to bridge a motor/sensory defect site. For motor nerves to regenerate, Schwann cells (SC) myelinate the newly grown axon. Sensory SCs have a reduced ability to produce myelin, partially explaining low success rates of autografts. This issue is masked in pre-clinical research by the excessive use of the rat sciatic nerve defect model, utilizing a mixed nerve with motor and sensory SCs. Aim of this study was to utilize extracorporeal shockwave treatment as a novel tool to influence SC phenotype. SCs were isolated from motor, sensory and mixed rat nerves and in vitro differences between them were assessed concerning initial cell number, proliferation rate, neurite outgrowth as well as ability to express myelin. We verified the inferior capacity of sensory SCs to promote neurite outgrowth and express myelin-associated proteins. Motor Schwann cells demonstrated low proliferation rates, but strongly reacted to pro-myelination stimuli. It is noteworthy for pre-clinical research that sciatic SCs are a strongly mixed culture, not representing one or the other. Extracorporeal shockwave treatment (ESWT), induced in motor SCs an increased proliferation profile, while sensory SCs gained the ability to promote neurite outgrowth and express myelin-associated markers. We demonstrate a strong phenotype commitment of sciatic, motor, and sensory SCs in vitro, proposing the experimental use of SCs from pure cultures to better mimic clinical situations. Furthermore we provide arguments for using ESWT on autografts to improve the regenerative capacity of sensory SCs.

- **Low-energy extracorporeal shock wave therapy promotes BDNF expression and improves functional recovery after spinal cord injury in rats** [39]

Low-energy extracorporeal shock wave therapy (ESWT) has been used to treat various human diseases. Previous studies have shown that low-energy ESWT promotes the release of various cell growth factors and trophic factors from the cells surrounding the target lesion. The aim of the current study was to determine whether the application of low-energy ESWT upregulates the expression of brain-derived

neurotrophic factor (BDNF) and reduces neural tissue damage and functional impairment using a rat model of thoracic spinal cord contusion injury. We found that low-energy ESWT promoted BDNF expression in the damaged neural tissue. The expression of BDNF was increased in various neural cells at the lesion. Additionally, low-energy ESWT increased the area of spared white matter and the number of oligodendrocytes in the injured spinal cord compared with untreated control animals. There were more axonal fibers around the injured site after the application of low-energy ESWT than control. Importantly, low-energy ESWT improved the locomotor functions evaluated by both the BBB scale and ladder rung walking test in addition to the sensory function measured using a von Frey test. Moreover, the electrophysiological assessment confirmed that the conductivity of the central motor pathway in the injured spinal cord was restored by low-energy ESWT. These findings indicate that low-energy ESWT promotes BDNF expression at the lesion site and reduces the neural tissue damage and functional impairment following spinal cord injury. Our results support the potential application of low-energy ESWT as a novel therapeutic strategy for treating spinal cord injury.

- **Inflammatory mediators are potential biomarkers for extracorporeal shockwave therapy in horses** [40]

Background: Extracorporeal shockwave therapy (ESWT) can potentially mask painful injuries in equine athletes. Tests to detect whether a horse has received ESWT prior to competition are needed. Extracorporeal shockwave therapy is known to affect inflammatory mediators in other species, and if these mediators are altered in the horse, these could serve as biomarkers of ESWT.
Objectives: To test the hypothesis that a single application of ESWT will alter the circulating protein concentrations of 10 inflammatory mediators in horse plasma.
Study design: Prospective repeated measures experimental study.
Methods: Eleven healthy horses were administered a single dose of ESWT on the dorsal surface of proximal MCIII. Blood samples were collected at -168, -144, -120, -96, -72, -70, -68, -66, -48, -24, -6, -4, -2, 0 h before and 2, 4, 6, 24, 48, 72, 96, 168, 336 and 504 h after ESWT. Plasma concentrations of interleukin 1 beta (IL-1β), IL-1 receptor antagonist (IL-1RA), IL-2, IL-4, IL-6, IL-10, IL-15, interferon gamma (IFN-γ), soluble toll-like receptor 2 (sTLR2) and tumour necrosis factor alpha (TNF-α) were measured to assess the effects of ESWT on these mediators.
Results: Baseline concentrations of inflammatory mediators did not change substantially during the week prior to ESWT. Plasma concentrations of five inflammatory factors changed following ESWT. IL-1β and IL-6 were significantly down-regulated ($P<0.01$), while TNF-α, IL-1RA and TLR2 were significantly up-regulated ($P<0.01$). The remaining cytokines were not significantly affected by ESWT.
Main limitations: This study was performed in a small number of sedentary, healthy pasture-kept horses using a single dose of ESWT applied to a single location. Additional studies are necessary to determine the effect of ESWT on inflammatory mediators in athletic horses undergoing treatment for musculoskeletal injuries.
Conclusions: Plasma concentrations of TNF-α, IL-1β, IL-1RA, IL-6 and TLR2 were significantly affected by ESWT, and deserve further investigation as possible biomarkers of ESWT.

- **miR-19a-3p containing exosomes improve function of ischemic myocardium upon shock wave therapy** [41]

Aims: As many current approaches for heart regeneration exert unfavourable side effects, the induction of endogenous repair mechanisms in ischaemic heart disease is of particular interest. Recently, exosomes carrying angiogenic miRNAs have been described to improve heart function. However, it remains challenging to stimulate specific release of reparative exosomes in ischaemic myocardium. In the present

study, we sought to test the hypothesis that the physical stimulus of shock wave therapy (SWT) causes the release of exosomes. We aimed to substantiate the pro-angiogenic impact of the released factors, to identify the nature of their cargo, and to test their efficacy in vivo supporting regeneration and recovery after myocardial ischaemia.

Methods and results: Mechanical stimulation of ischaemic muscle via SWT caused extracellular vesicle (EV) release from endothelial cells both in vitro and in vivo. Characterization of EVs via electron microscopy, nanoparticle tracking analysis and flow cytometry revealed specific exosome morphology and size with the presence of exosome markers CD9, CD81, and CD63. Exosomes exhibited angiogenic properties activating protein kinase b (Akt) and extracellular-signal regulated kinase (ERK) resulting in enhanced endothelial tube formation and proliferation. A miRNA array and transcriptome analysis via next-generation sequencing were performed to specify exosome content. miR-19a-3p was identified as responsible cargo, antimir-19a-3p antagonized angiogenic exosome effects. Exosomes and target miRNA were injected intramyocardially in mice after left anterior descending artery ligation. Exosomes resulted in improved vascularization, decreased myocardial fibrosis, and increased left ventricular ejection fraction as shown by transthoracic echocardiography.

Conclusion: The mechanical stimulus of SWT causes release of angiogenic exosomes. miR-19a-3p is the vesicular cargo responsible for the observed effects. Released exosomes induce angiogenesis, decrease myocardial fibrosis, and improve left ventricular function after myocardial ischaemia. Exosome release via SWT could develop an innovative approach for the regeneration of ischaemic myocardium.

- **Extracorporeal shock wave therapy decreases COX-2 by inhibiting TLR4-NFκB pathway in a prostatitis rat model** [42]

Background: This study aims to evaluate the effect of extracorporeal shock wave therapy (ESWT) on chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and to explore the mechanism.

Methods: RWPE-2 cells were randomly divided into three groups: (a) RWPE-2 group (normal control), (b) LPS groups (lipopolysaccharide inducing inflammation) and (c) ESWT groups (LPS induced RWPE-2 treated by ESWT). After ESWT was administered, cells and supernatant were collected for enzyme-linked immunosorbent assay (ELISA) and Western blot analysis. In vivo, Sprague-Dawley rats (n = 30) were randomly divided into three groups: (a) normal control group, (b) prostatitis groups, and (c) ESWT groups. Prostatitis rats were induced by 17 β-estradiol and dihydrotestosterone for 4 weeks. After ESWT, prostates of each group were collected for immunohistochemistry, Western blot analysis, and ELISA.

Results: ESWT improved prostatitis by attenuating inflammation ($P < .01$). ESWT downregulated the expression of cyclooxygenase 2 (COX-2) through inhibiting TLR4-NFκB pathway compared with the LPS group in vitro or prostatitis group in vivo ($P < .05$). TRAF2 mediates ERK1/2-COX2 pathway. ESWT promotes prostate tissue recovery by stimulating vascular endothelial growth factor expression ($P < .01$). ESWT could suppress apoptosis in the prostate.

Conclusions: ESWT improved CP/CPPS and reduced inflammation by degrading COX-2 in microenvironment through TLR4-NFκB-inhibiting pathway. TRAF2 regulator in ERK1/2-COX-2 inhibition significantly reduced inflammation, thus suggesting ESWT may be a potential and promising treatment for CP/CPPS.

- **Long-term functional change of cryoinjury-induced detrusor underactivity and effects of extracorporeal shock wave therapy in a rat model** [43]

Purpose: To investigate the long-term functional change of cryoinjury-induced detrusor underactivity (DU) and the therapeutic potential of repeated low-energy shock wave therapy (LESW).

Methods: Fifty-six female Sprague-Dawley rats were assigned into sham and cryoinjury of bladder with or without LESW (0.05 or 0.12 mJ/mm^2; 200 pulses; twice a week for 2 weeks after cryoinjury). Under halothane anesthesia, an incision was made in lower abdomen, and cryoinjury was provoked by bilateral placement of a chilled aluminum rod on the bladder filled with 1 ml saline. Measurement of contractile responses to KCl and carbachol in vitro, conscious voiding, and histological and protein changes were performed on week 1, 2, and 4 after cryoinjury.
Results: Cryoinjury of bladder induced a significant decrease in the detrusor contraction amplitude at week 1 (55.0%) and week 2 (57.2%), but the decrease in the contractile response to KCl and carbachol was only noted at week 1. At week 1, significantly increased COX-2 and TGF-β1 expression accompanied a decrease of VEGF and CGRP expression. At week 4, there was a partial recovery of voiding function and a significant increase in the Ki-67 staining. LESW treatment at higher energy level further amplified the Ki-67 staining and improved the recovery of contraction amplitude and the expression of TGF-β1 and VEGF.
Conclusions: Cryoinjury of detrusor induces DU/UAB with functional impairment lasting for up to 4 weeks, but the associated molecular changes are restored by 2 weeks. LESW improved bladder wall composition, and hastened functional recovery from cryoinjury.

❖ **Long-term Therapeutic Effects of Extracorporeal Shock Wave-Assisted Melatonin Therapy on Mononeuropathic Pain in Rats** [44]

We evaluated the ability of extracorporeal shock wave (ECSW)-assisted melatonin (Mel) therapy to offer an additional benefit for alleviating the neuropathic pain (NP) in rats. Left sciatic nerve was subjected to chronic constriction injury (CCI) to induce NP. Animals (n = 30) were randomized into group 1 (sham-operated control), group 2 (CCI only), group 3 (CCI + ECSW), group 4 (CCI + Mel) and group 5 (CCI + ECSW + Mel). By days 15, 22 and 29 after CCI, the thermal paw withdrawal latency (TPWL) and mechanical paw withdrawal threshold (MPWT) were highest in group 1, lowest in group 2, significantly higher in group 5 than in groups 3 and 4, but they showed no difference between the later two groups (all $p < 0.0001$). The protein expressions of inflammatory (TNF-α, NF-κB, MMP-9, IL-1ß), oxidative-stress (NOXs-1, -2, -4, oxidized protein), apoptotic (cleaved-caspase3, cleaved-PARP), DNA/mitochondrial-damaged (γ-H2AX/cytosolic-cytochrome C), microglia/astrocyte activation (ox42/GFAP), and MAPKs [phosphorylated (p)-p38, p-JNK, p-ERK] biomarkers in dorsal root ganglia neurons (DRGs) and in spinal dorsal horn were exhibited an opposite pattern of TPWL among the five groups (all $p < 0.0001$). Additionally, protein expressions of Nav.1.3, Nav.1.8 and Nav.1.9 in sciatic nerve exhibited an identical pattern to inflammation among the five groups (all $p < 0.0001$). The numbers of cellular expressions of MAPKs (p-ERK1/2+/peripherin + cells, p-ERK1/2+/NF200 + cells and p-JNK+/peripherin + cells, p-JNK+/NF200 + cells) and voltage-gated sodium channels (Nav.1.8+/peripherin + cells, Nav.1.8+/NF200 + cells, Nav.1.9+/peripherin + cells, Nav.1.9+/NF200 + cells) in small and large DRGs displayed an identical pattern to inflammation among the five groups (all $p < 0.0001$). In conclusion, the synergistic effect of combined ECSW-Mel therapy is superior to either one alone for long-term improvement of mononeuropathic pain-induced by CCI in rats.

❖ **Low Energy Shock Wave Therapy Inhibits Inflammatory Molecules and Suppresses Prostatic Pain and Hypersensitivity in a Capsaicin Induced Prostatitis Model in Rats** [45]

The effect of low energy shock wave (LESW) therapy on the changes of inflammatory molecules and pain reaction was studied in a capsaicin (10 mM, 0.1 cc) induced prostatitis model in rats. Intraprostatic capsaicin injection induced a pain reaction, including closing of the eyes, hypolocomotion, and tactile allodynia, which effects were ameliorated by LESW treatment. LESW therapy (2Hz, energy flux density of 0.12 mJ/mm2) at 200 and 300 shocks significantly decreased capsaicin-induced inflammatory reactions,

reflected by a reduction of tissue edema and inflammatory cells, COX-2 and TNF-α stained positive cells, however, the therapeutic effects were not observed at 100 shocks treated group. Capsaicin-induced IL-1β, COX-2, IL-6, caspase-1, and NGF upregulation on day 3 and 7, while NALP1 and TNF-α upregulation was observed on day 7. LESW significantly suppressed the expression of IL-1β, COX-2, caspase-1, NGF on day 3 and IL-1β, TNF-α, COX-2, NALP1, caspase-1, NGF expression on day 7 in a dose-dependent fashion. LESW has no significant effect on IL-6 expression. Intraprostatic capsaicin injection activates inflammatory molecules and induces prostatic pain and hypersensitivity, which effects were suppressed by LESW. These findings might be the potential mechanisms of LESW therapy for nonbacterial prostatitis in humans.

❖ Shock Wave Treatment After Hindlimb Ischaemia Results in Increased Perfusion and M2 Macrophage Presence [32]

Shock wave therapy (SWT) has been shown to induce angiogenesis in ischaemic muscle. However, the mechanism of action remains unknown. Macrophages are crucial for angiogenic responses after ischaemic injury. The M2 macrophage subset enables tissue repair and induces angiogenesis. It was hypothesized that the angiogenic effects of SWT are at least partly caused by enhanced macrophage recruitment. C57BL/6 mice were subjected to hind limb ischaemia with subsequent SWT or sham treatment. Muscles were analysed via immunofluorescence staining, reverse-transcription polymerase chain reaction and western blot. Gene expression and proteins involved in macrophage recruitment were analysed and tissue sections were stained for macrophages, including subsets, capillaries and arterioles. Laser Doppler perfusion imaging was performed to assess functional outcome. Treated muscles showed increased expression of the pivotal macrophage recruiting factor monocyte chemotactic protein 1 (MCP-1). Higher levels of macrophage marker CD14 were found. Increased numbers of macrophages after SWT could be confirmed by immunofluorescence staining. The expression of the M2 polarization promoting chemokine interleukin 13 was significantly elevated in the treatment group. Elevated mRNA expression of the M2 scavenger receptor CD163 was found after SWT. Immunofluorescence staining confirmed increased numbers of M2 macrophages after treatment. It was found that SWT resulted in higher number of capillaries and arterioles. Assessment of functional outcome revealed significantly improved limb perfusion in treated animals. Shock wave therapy causes increased macrophage recruitment and enhanced polarization towards reparative M2 macrophages in ischaemic muscle resulting in angiogenesis and improved limb perfusion and therefore represents a promising new treatment option for the treatment of ischaemic heart disease.

❖ Extracorporeal shockwave against inflammation mediated by GPR120 receptor in cyclophosphamide-induced rat cystitis model [46]

Background: We tested the hypothesis that extracorporeal shockwave treatment (ESWT) can abolish inflammation and restore urothelial barrier integrity in acute interstitial cystitis by upregulating the fatty acid receptor GPR120.
Methods: A total of 30 female Sprague-Dawley rats were categorized into five groups: (1) sham-operated rats (SC); (2) rats treated with ESWT (SC + ESWT); (3) rats with bladder irritation using 150 mg/kg cyclophosphamide through intraperitoneal injection; (4) cyclophosphamide rats treated with ESWT (cyclophosphamide+ESWT); (5) cyclophosphamide rats treated with GPR120 agonist (cyclophosphamide+GW9508).
Results: On Day 3, urine and bladder specimens were collected for biochemical, histopathological, immunological, and immunoblotting analysis. Following stimulation with cyclophosphamide, the inhibition of the elevated levels of TAK1/NF-κB and phospho-TAK1/NF-κB by ESWT and GPR120 agonists in RT4 cells was associated with a suppression of NF-κB translocation from the cytosol to the nucleus.

Accordingly, this anti-inflammatory effect was abolished by GPR120 antagonist and knockdown of GPR120. Histologically, bladder inflammation in cyclophosphamide-treated rats was suppressed by GW9508 or ESWT. Masson's trichrome and Sirius red staining revealed that cyclophosphamide treatment enhanced synthesis of extracellular matrix in rats that was reversed by GW9508 or ESWT. Upregulated pro-inflammatory mediators and cytokines in the cyclophosphamide-treated rats were also suppressed in the GW9508- or ESWT-treated rats. The significantly increased inflammatory cell infiltration as well as the impaired urothelial integrity of the bladder after cyclophosphamide treatment were reversed by treatment with GW9508 or ESWT.
Conclusions: These findings suggest that GPR120, the sensing receptor for ESWT, may be useful in the treatment of interstitial cystitis by inhibiting inflammatory response in bladder cells.

- **Low-Intensity Extracorporeal Shock Wave Therapy Enhances Brain-Derived Neurotrophic Factor Expression through PERK/ATF4 Signalling Pathway** [47]

Low-intensity extracorporeal shock wave therapy (Li-ESWT) is used in the treatment of erectile dysfunction, but its mechanisms are not well understood. Previously, we found that Li-ESWT increased the expression of brain-derived neurotrophic factor (BDNF). Here we assessed the underlying signaling pathways in Schwann cells in vitro and in penis tissue in vivo after nerve injury. The result indicated that BDNF were significantly increased by the Li-ESWT after nerve injury, as well as the expression of BDNF in Schwann cells (SCs, RT4-D6P2T) in vitro. Li-ESWT activated the protein kinase RNA-like endoplasmic reticulum (ER) kinase (PERK) pathway by increasing the phosphorylation levels of PERK and eukaryotic initiation factor 2a (eIF2α), and enhanced activating transcription factor 4 (ATF4) in an energy-dependent manner. In addition, GSK2656157-an inhibitor of PERK-effectively inhibited the effect of Li-ESWT on the phosphorylation of PERK, eIF2α, and the expression of ATF4. Furthermore, silencing ATF4 dramatically attenuated the effect of Li-ESWT on the expression of BDNF, but had no effect on hypoxia-inducible factor (HIF)1α or glial cell-derived neurotrophic factor (GDNF) in Schwann cells. In conclusion, our findings shed new light on the underlying mechanisms by which Li-ESWT may stimulate the expression of BDNF through activation of PERK/ATF4 signaling pathway. This information may help to refine the use of Li-ESWT to further improve its clinical efficacy.

- **Effects of low energy shock wave therapy on inflammatory moleculars, bladder pain, and bladder function in a rat cystitis model** [48]

Aims: Low energy shock wave (LESW) is known to facilitate tissue regeneration with analgesic and anti-inflammatory effects. We examined the effects of LESW on the expression of inflammatory molecules, pain behavior, and bladder function in a rat cystitis model.
Methods: Control and experimental animals were injected with saline or cyclophosphamide (CYP; 75 mg/kg intraperitoneally) on day 1 and 4. After lower midline incision, the bladders were exposed to LESW (300 pulses, 0.12 mJ/mm^2) or sham operation on day 2. In study 1 (N = 12, 4 for each group), the nociceptive effects of CYP were evaluated for 30 min by behavioral assessment on day 4 one hour after CYP injection. In study 2 (N = 21, 7 for each group), continuous cystometry (CMG) was performed on day 8. The bladder was harvested after behavioral assessment or CMG for histology and Western blotting.
Results: CYP-induced upregulation of COX2 and IL6 expression, caused pain behavior (eye closing and hypolocomotion), and bladder inflammation was noted on days 4 and 8 along with bladder hyperactivity. LESW treatment reduced pain behavior and downregulated the NGF expression (33.3%, $P < 0.05$) on day 4 and IL6 (40.9%, $P < 0.05$). LESW treatment suppressed bladder overactivity (intercontraction interval 77.8% increase, $P < 0.05$) by decreasing inflammation and COX2 (38.6%, $P < 0.05$) expression and NGF expression (25.2%, $P = 0.0812$).

Conclusions: CYP-induced bladder pain, inflammation, and overactivity involves activation of IL6, NGF, and COX2 expression. These changes are suppressed by LESW, indicating it as a potential candidate for relieving bladder inflammatory conditions and overactivity.

❖ Toll-like Receptor 3 Signalling Mediates Response upon Shock Wave Treatment of Ischaemic Muscle [49]

Aims: Shock wave therapy (SWT) represents a clinically widely used angiogenic and thus regenerative approach for the treatment of ischaemic heart or limb disease. Despite promising results in preclinical and clinical trials, the exact mechanism of action remains unknown. Toll-like receptor 3, which is part of the innate immunity, is activated by binding double-stranded (ds) RNA. It plays a key role in inflammation, a process that is needed also for angiogenesis. We hypothesize that SWT causes cellular cavitation without damaging the target cells, thus liberating cytoplasmic RNA that in turn activates TLR3.
Methods and results: SWT induces TLR3 and IFN-β1 gene expression as well as RNA liberation from endothelial cells in a time-dependant manner. Conditioned medium from SWT-treated HUVECs induced TLR3 signalling in reporter cells. The response was lost when the medium was treated with RNase III to abolish dsRNAs or when TLR3 was silenced using siRNAs. In a mouse hind limb ischaemia model using wt and TLR3(-/-) mice (n = 6), SWT induced angiogenesis and arteriogenesis only in wt animals. These effects were accompanied by improved blood perfusion of treated limbs. Analysis of main molecules of the TLR3 pathways confirmed TLR3 signalling in vivo following SWT.
Conclusion: Our data reveal a central role of the innate immune system, namely Toll-like receptor 3, to mediate angiogenesis upon release of cytoplasmic RNAs by mechanotransduction of SWT.

❖ The Influence of Shockwave Therapy on Orthodontic Tooth Movement Induced in the Rat [50]

Shockwave therapy is used in medicine due to its ability to stimulate healing processes. The application of orthodontic force evokes an inflammatory reaction resulting in tooth movement. Shockwave therapy might have an effect on both inflammatory and periodonal ligament cytokine profiles. Our aim was to evaluate the fluctuations of different inflammatory cytokines after orthodontic force induction with and without shockwave therapy. An orthodontic appliance was applied between the rats' molars and incisors. In conjunction with the commencement of orthodontic force, the rats were treated with a single episode of 1000 shock waves and the gingival crevicular fluid was collected for 3 days. The expression and concentration of different cytokines was evaluated by a commercial 4-multiplex fluorescent bead-based immunoassay. The level of all cytokines displayed a similar trend in both shockwave-treated and untreated groups; the concentration peaked on the first day and declined thereafter. In all cases, however, the cytokine levels were smaller in the shockwave-treated than in untreated animals; a significant difference was found for sRANKL and borderline difference for IL-6 on Day 1. We conclude that shockwave therapy during the induction of orthodontic tooth movement influences the expression of inflammatory cytokines.

❖ Effects of Shock Waves on Expression of IL-6, IL-8, MCP and TNF-α Expression by Human Periodontal Ligament Fibroblasts: an In Vitro Study [51]

Background: Extracorporeal shock wave therapy (ESWT) can modulate cell behavior through mechanical information transduction. Human periodontal ligament fibroblasts (hPDLF) are sensible to mechanical stimulus and can express pro-inflammatory molecules in response. The aim of this study was to evaluate the impacts of shock waves on interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor-alpha (TNF-α) expression by hPDLF.

Material/methods: After being treated by shock waves with different parameters (100-500 times, 0.05-0.19 mJ/mm(2)), cell viability was tested using CCK-8. IL-6, IL-8, MCP-1, and TNF-α gene expression was analyzed by quantitative real-time polymerase chain reaction (qRT-PCR) and IL-6 and IL-8 protein was measured by enzyme-linked immunosorbent assay (ELISA) at different time points.
Results: Shock waves with the parameters used in this study had no significant effects on the viability of hPDLF. A statistical inhibition of IL-6, IL-8, MCP-1, and TNF-α expression during the first few hours was observed (P<0.05). Expression of IL-8 was significantly elevated in the group receiving the most pulses of shock wave (500 times) after 4 h (P<0.05). At 8 h and 24 h, all treated groups demonstrated significantly enhanced IL-6 expression (P<0.05). TNF-α expression in the groups receiving more shock pulses (300, 500 times) or the highest energy shock treatment (0.19 mJ/mm(2)) was statistically decreased (P<0.05) at 24 h.
Conclusions: Under the condition of this study, a shock wave with energy density no higher than 0.19 mJ/mm(2) and pulses no more than 500 times elicited no negative effects on cell viability of hPDLF. After a uniform initial inhibition impact on expression of inflammatory mediators, a shock wave could cause dose-related up-regulation of IL-6 and IL-8 and down-regulation of TNF-α.

❖ Shock Wave Treatment Protects From Neuronal Degeneration via a Toll-Like Receptor 3 Dependent Mechanism: Implications of a First-Ever Causal Treatment for Ischemic Spinal Cord Injury [52]

Background: Paraplegia following spinal cord ischemia represents a devastating complication of both aortic surgery and endovascular aortic repair. Shock wave treatment was shown to induce angiogenesis and regeneration in ischemic tissue by modulation of early inflammatory response via Toll-like receptor (TLR) 3 signaling. In preclinical and clinical studies, shock wave treatment had a favorable effect on ischemic myocardium. We hypothesized that shock wave treatment also may have a beneficial effect on spinal cord ischemia.
Methods and results: A spinal cord ischemia model in mice and spinal slice cultures ex vivo were performed. Treatment groups received immediate shock wave therapy, which resulted in decreased neuronal degeneration and improved motor function. In spinal slice cultures, the activation of TLR3 could be observed. Shock wave effects were abolished in spinal slice cultures from TLR3(-/-) mice, whereas the effect was still present in TLR4(-/-) mice. TLR4 protein was found to be downregulated parallel to TLR3 signaling. Shock wave-treated animals showed significantly better functional outcome and survival. The protective effect on neurons could be reproduced in human spinal slices.
Conclusions: Shock wave treatment protects from neuronal degeneration via TLR3 signaling and subsequent TLR4 downregulation. Consequently, it represents a promising treatment option for the devastating complication of spinal cord ischemia after aortic repair.

❖ Effect of shock waves on macrophages: A possible role in tissue regeneration and remodeling [53]

Introduction: Extracorporeal Shock Wave Therapy (ESWT) is broadly used as a non-surgical therapy in various diseases for its pro-angiogenic and anti-inflammatory effects. However, the molecular mechanisms translating tissue exposure to shock waves (SW) in a biological response with potential therapeutic activity are largely unknown. As macrophages take part in both the onset and amplification of the inflammatory response, and well in its resolution, we investigated the effect of SW on their biology.
Methods: Human monocyte-derived macrophages were polarized to classic (M1) pro-inflammatory macrophages or alternative (M2) anti-inflammatory macrophages and exposed to SW ad different intensities. Expression levels of marker genes of macrophage activation were measured by qPCR at different time points.

Results: SW did not induce activation of resting macrophages at any energy level used. Conversely, when used at low energy SW caused a significant inhibition of some M1 marker genes (CD80, COX2, CCL5) in M1 macrophages and a significant synergistic effect for some M2 marker genes (ALOX15, MRC1, CCL18) in M2 macrophages. SW also affected cytokine and chemokine production, inducing in particular a significant increase in IL-10 and reduction in IL-1β production.
Conclusions: Macrophage exposure to low energy SW dampens the induction of the pro-inflammatory profile characterizing M1 macrophages and promotes the acquisition of an anti-inflammatory profile synergizing with macrophage alternative activation.

- **Alteration of Inflammatory Response by Shock Wave Therapy Leads to Reduced Calcification of Decellularized Aortic Xenografts in Mice** [54]

Objectives: Tissue-engineered xenografts represent a promising treatment option in heart valve disease. However, inflammatory response leading to graft failure and incomplete in vitro repopulation with recipient cells remain challenging. Shock waves (SWs) were shown to modulate inflammation and to enhance re-epithelialization. We therefore aimed to investigate whether SWs could serve as a feasible adjunct to tissue engineering.
Methods: Porcine aortic pieces were decellularized using sodium deoxycholate and sodium dodecylsulphate and implanted subcutaneously into C57BL/6 mice (n = 6 per group). The treatment (shock wave therapy, SWT) group received SWs (0.1 mJ/mm(2), 500 impulses, 5 Hz) for modulation of inflammatory response directly after implantation; control animals remained untreated (CTR). Grafts were harvested 72 h and 3 weeks after implantation and analysed for inflammatory cytokines, macrophage infiltration and polarization, osteoclastic activity and calcification. Transmission electron microscopy (TEM) was performed. Endothelial cells (ECs) were treated with SWs and analysed for macrophage regulatory cytokines. In an ex vivo experimental set-up, decellularized porcine aortic valve conduits were reseeded with ECs with and without SWT (0.1 mJ/mm(2), 300 impulses, 3 Hz), fibroblasts as well as peripheral blood mononuclear cells (all human) and tested in a pulsatile flow perfusion system for cell coverage.
Results: Treated ECs showed an increase of macrophage migration inhibitory factor and macrophage inflammatory protein 1β, whereas CD40 ligand and complement component C5/C5a were decreased. Subcutaneously implanted grafts showed increased mRNA levels of tumour necrosis factor α and interleukin 6 in the treatment group. Enhanced repopulation with recipient cells could be observed after SWT. Augmented macrophage infiltration and increased polarization towards M2 macrophages was observed in treated animals. Enhanced recruitment of osteoclastic cells in proximity to calcified tissue was found after SWT. Consequently, SWT resulted in decreased areas of calcification in treated animals. The reseeding experiment revealed that fibroblasts showed the best coverage compared with other cell types. Moreover, SW-treated ECs exhibited enhanced repopulation compared with untreated controls.
Conclusions: SWs reduce the calcification of subcutaneously implanted decellularized xenografts via the modulation of the acute macrophage-mediated inflammatory response and improves the in vitro repopulation of decellularized grafts. It may therefore serve as a feasible adjunct to heart valve tissue engineering.

- **Selective loss of unmyelinated nerve fibers after extracorporeal shockwave application to the musculoskeletal system** [21]

Application of extracorporeal shockwaves (ESW) to the musculoskeletal system may induce long-term analgesia in the treatment of chronic tendinopathies of the shoulder, heel and elbow. However, the molecular and cellular mechanisms behind this phenomenon are largely unknown. Here we tested the

hypothesis that long-term analgesia caused by ESW is due to selective loss of nerve fibers in peripheral nerves. To test this hypothesis in vivo, high-energy ESW were applied to the ventral side of the right distal femur of rabbits. After 6 weeks, the femoral and sciatic nerves were investigated at the light and electron microscopic level. Application of ESW resulted in a selective, substantial loss of unmyelinated nerve fibers within the femoral nerve of the treated hind limb, whereas the sciatic nerve of the treated hind limb remained unaffected. These data might indicate that alleviation of chronic pain by selective partial denervation may play an important role in the effects of clinical ESW application to the musculoskeletal system.

- **Extracorporeal shockwave application to the distal femur of rabbits diminishes the number of neurons immunoreactive for substance P in dorsal root ganglia L5** [22]

Application of extracorporeal shockwaves to the musculoskeletal system can induce long-term analgesia in the treatment of chronic painful diseases such as calcifying tendonitis of the shoulder, tennis elbow and chronic plantar fasciitis. However, the molecular and cellular mechanisms underlying this phenomenon are largely unknown. Recently it was shown that application of extracorporeal shockwaves to the distal femur of rabbits can lead to reduced concentration of substance P in the shockwaves' focal zone. In the present study we investigated the impact of extracorporeal shockwaves on the production of substance P within dorsal root ganglia in vivo. High-energy shockwaves were applied to the ventral side of the right distal femur of rabbits. After six weeks, the dorsal root ganglia L5 to L7 were investigated with high-precision design-based stereology. The application of extracorporeal shockwaves caused a statistically significant decrease in the mean number of neurons immunoreactive for substance P within the dorsal root ganglion L5 of the treated side compared with the untreated side, without affecting the total number of neurons within this dorsal root ganglion. No effect was observed in the dorsal root ganglia L6 and L7, respectively. These data might further contribute to our understanding of the molecular and cellular mechanisms in the induction of long-term analgesia by extracorporeal shockwave application to the musculoskeletal system.

- **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** [30]

Objective: To evaluate the effect of focused extracorporeal shock wave therapy (ESWT) and radial pressure wave therapy (RPWT) on immunohistochemical staining for substance P and calcitonin gene-related peptide (CGRP) in the skin and periosteum of sheep.
Animals: 36 sheep.
Procedures: All 4 limbs of 36 sheep were treated with ESWT, RPWT, or a sham treatment. For 14 days after treatment, at least 2 sheep were euthanized daily and tissue was harvested for histologic evaluation of nerves via staining for substance P and CGRP in the skin and periosteum.
Results: No effects of ESWT or RPWT were observed on the number of nerves with stain uptake for substance P or CGRP in the skin or periosteum.
Conclusions and clinical relevance: Substance P- and CGRP-containing nerve fibers are not disrupted by EWST or RPWT. Further studies are needed to identify the mechanism of analgesia observed in association with these treatment modalities.

- **Evaluation of analgesia resulting from extracorporeal shock wave therapy and radial pressure wave therapy in the limbs of horses and sheep** [31]

Objective: To identify the duration and potential mechanisms of analgesia following extracorporeal shock wave therapy (ESWT) and radial pressure wave therapy (RPWT) in limbs of horses and sheep.

Animals: 6 horses and 30 sheep.
Procedure: An electrical stimulus was used to identify the nociceptive threshold for each horse daily for 3 days before treatment (baseline) with ESWT or RPWT, 8 hours after treatment, and at 24-hour intervals for 7 days after treatment. Testing was conducted for the treatment field (midmetacarpus or midmetatarsus) and nerve field (medial and lateral forelimb heel bulbs) distal to a treatment site that included the nerve on the abaxial surface of the proximal sesamoid bone. All 4 limbs of 30 sheep were treated with ESWT, RPWT, or a sham treatment. Two sheep were euthanatized daily and tissue harvested for histologic evaluation of nerves, and concentrations of substance P and calcitonin gene-related peptide were measured in the skin and periosteum.
Results: Values did not differ significantly between baseline and after treatment for the treatment field or nerve field sensation. There was a large difference in the slope when data for horses were plotted for the first 3 days after treatment, compared with the slope for days 4 to 7 after treatment. No differences were found in neuropeptide concentrations after treatment of the sheep, but there was an inflammatory response in the treated nerves.
Conclusions and clinical relevance: A small cutaneous analgesic effect may exist at the treatment site for approximately 3 days after ESWT or RPWT in horses.

- **Application of shock waves to rat skin decreases calcitonin gene-related peptide immunoreactivity in dorsal root ganglion neurons** [28]

There have been several reports on the use of extracorporeal shock waves in the treatment of pseudarthrosis, calcifying tendinitis, and tendinopathies of the elbow. However, the pathomechanism of pain relief has not been clarified. To investigate the analgesic properties of shock wave application, we analyzed changes in calcitonin gene-related peptide (CGRP)-immunoreactive (ir) dorsal root ganglion (DRG) neurons. In the nontreated group, fluorogold-labeled dorsal root ganglion neurons innervating the most middle foot pad of hind paw were distributed in the L4 and L5 dorsal root ganglia. Of these neurons, 61% were CGRP-ir. However, in the shock wave-treated group, the percentage of FG-labeled CGRP-ir DRG neurons decreased to 18%. These data show that relief of clinical pain after shock wave application may result from reduced CGRP expression in DRG neurons.

- **Absence of spinal response to extracorporeal shock waves on the endogenous opioid systems in the rat** [55]

Extracorporeal shock wave therapy (ESWT) seems to be a new therapeutic strategy for chronic pain due to tendopathies. Neurophysiological mechanisms of action for pain relief following ESWT are still unknown. The aim of this study was to investigate if the analgesic effect of ESWT is caused by modulation of the endogenous spinal opioid system. Rats were treated with two different energy flux densities (0.04 and 0.11mJ/mm(2)) and immunohistochemical analysis of met-enkephalin (MRGL) and dynorphin (Dyn) was performed at 4 or 72 h after ESWT. ESWT had no modulatory influence on the expression of the spinal opioid systems. Different energy doses or repetitive treatment did not alter MRGL or Dyn immunoreactivity in the spinal cord. Furthermore, a delayed effect of ESWT at 72 h after treatment was not detectable. We conclude from these findings that the analgesic effects of ESWT treatment are not supported by endogenous opioids.

- **No influence of low-energy extracorporeal shock wave therapy (ESWT) on spinal nociceptive systems** [29]

The analgesic effects of high-energy extracorporeal shock wave therapy (ESWT) were discovered by chance during its application for urolithiasis and for bone pseudarthrosis. Despite the extensive use of

ESWT, the mechanisms of its antinociceptive effects are still unclear. A gate control mechanism and other antinociceptive mechanisms have been postulated. The aim of this study was to investigate the possible influence of low-energy ESWT on the expression of the transmitters substance P (SP) and calcitonin gene-related peptide (CGRP) in the lumbar spinal cord of the rat. Immunohistochemical analysis of the expression of the neuropeptides CGRP and SP was performed in rats treated either once with 1000 impulses or three times with 1000 impulses, with two different energy flux densities being used (0.043 and 0.11 mJ/mm2). The animals were killed either 4 or 72 h after the ESWT. No regulatory effect of ESWT on the expression of SP or CGRP in the dorsal horns was found. Because the application of ESWT showed no significant changes in the sensory system, it is unlikely that the application of ESWT triggers the endogenous pain control system of the rat through hyperstimulation analgesia. Furthermore, these results show that low-energy ESWT had no side effects on the rat spinal cord.

❖ **Unchanged c-Fos expression after extracorporeal shock wave therapy: an experimental investigation in rats** [56]

Background: Despite the extensive use of extracorporeal shock wave therapy (ESWT) in the therapy of chronic tendopathies, the biological mechanisms of its antinociceptive effects are still unclear.

Methods: In this study we addressed the question of whether the clinically described, long-lasting effect of ESWT is mediated by changes in the activity of spinal cord neurones. As a marker for neuronal activity which is also able to interfere with the molecular expression pattern of neurones, the expression of the inducible transcription factor c-Fos was analysed in the animal model of the rat. Despite application of different energy levels, the analysis of c-Fos protein expression at an early (4 h) and late (72 h) time point after ESWT revealed no visible changes in immunoreactivity in the dorsal horn of the spinal cord. Additionally, there was no change in c-Fos protein and its gene expression c-Fos mRNA in the treatment area of the paw.

Results and conclusion: We conclude that ESWT with an energy flux dose up to 0.33 mJ/mm(2)does not modify neuronal activity. Since the application of ESWT showed no significant changes in the immunoreactivity of c-Fos, it is therefore unlikely that ESWT triggers stimulation-produced analgesia via activation of peripheral nerves.

5.2. Clinical Evidence – Pain Relief Acute and Neuropathic Pain

Note: **Although difficult to measure, due to ist multifaceted and subjective nature, pain is the primary endpoint for most investigations. In the course of pain management and analysis special pain rating scales and pain questionnaires are used.**

Note: **Reference titles written in dark blue text colour were performed with TRT/MTS SoftWave™ Technology.**

Cross selection of thematically relevant publications:

❖ **Efficacy of Unfocused Medium-Intensity Extracorporeal Shock Wave Therapy (MI-ESWT) for Plantar Fasciitis** [57]

Weill Medical College of Cornell University, New York, NY

Extracorporeal shock wave therapy (ESWT) is a promising treatment for plantar fasciitis (PF), however treatment results have varied due to inconsistencies among types of shock waves treatment and devices used. This retrospective chart review includes patients who underwent EWST using the OrthoGold 100™

shock wave device (MTS, Konstanz, Germany) for PF between January, 2013 and September, 2018. There were 108 patients (119 heels) identified, with a mean age of 51.7 ± 16.5 (Range 21-83) years. Patients were treated weekly for 3 weeks, with 2000 impulses per session at an energy flux density (EFD) between 0.10 and 0.17 mJ/mm ^{2}. Mean follow-up duration was 11.5 ± 9.7 (Range 3-51) months. Mean pre-ESWT pain visual assessment scale (VAS) improved from 6.7 ± 1.7 to 2.6 ± 2.7 (p< 0.001). The Foot and Ankle Outcome Score (FAOS) subscales: pain, function of daily living, function of sports and recreational activities and quality of life domains improved from 53.7 ± 14.9 to 75.7 ± 16.7 (p< 0.001), from 38 ± 15.2 to 71.8 ± 23 (p< 0.001), from 55.8 ± 16.4 to 71.4 ± 18 (p< 0.001), from 42.4 ± 21.5 to 59.4 ± 20.3 (p< 0.001) and from 44.9 ± 16.4 to 69 ± 23.9 (p< 0.001), respectively. Eighty-eight patients (81.5%) were satisfied with the procedure at final follow-up. Treatment of plantar fasciitis with unfocused shock waves was well tolerated and led to significant pain reduction, functional improvement and patient satisfaction.

❖ **The Effects Of Extracorporeal Shock Wave Therapy On Pain, Disability And Life Quality Of Chronic Low Back Pain Patients** [58]

Background: Low back pain is the most common form of pain related to the musculoskeletal system disorders. ESWT has been suggested as a new treatment modality in CLBP and its effectiveness has been investigated in a small number of studies.
Objective: The aim of this study is to investigate the effect of Extracorporeal Shockwave Therapy (ESWT) on pain, functional status, and quality of life compared to placebo in chronic low back pain (CLBP) patients.
Methods/design: Prospective, randomized, placebo-controlled, double-blind study.
Setting: The study occurred at the University Of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Physical Medicine and Rehabilitation (Bursa, Turkey).
Participants: Participants were 45 patients with CLBP.
Interventions: Participants were randomized into 2 groups. Group 1 (n = 25) received ESWT and Group 2 (n = 20) received placebo ESWT.
Primary outcome measures: The patients were assessed by using Numerical Rating Scale (NRS), Oswestry Disability Index (ODI), Hospital Anxiety and Depression Scale (HADS), Short-form 36 (SF-36). The data were obtained before treatment (W0), at sixth (W6) and twelfth week (W12).
Results: In Group 1, statistically significant improvement was found in all parameters of rest and movement NRS, ODI, HADS and SF-36 except for emotional role at both W6 and W12 compared to W0(P < .05). Comparison of the difference scores of the two groups showed significantly superior improvement in Group 1 for all parameters at both W6 and W12 (P < .05).
Conclusions: The results of our study have shown that ESWT had a statistically significant superiority over placebo for improvement in the parameters of pain, disability, depression, anxiety, and quality of life in the patients with CLBP.

❖ **Retrospective Chart Review of Treatment Outcome Following Low-Intensity Shockwave Therapy for the Treatment of Vestibulodynia with Urogold100** [59]

San Diego Sexual Medicine, APC.

Introduction: Genital pain disorders have devastating effects on a woman's quality of life, including social isolation. These disorders occur with high prevalence; more than 1/3 of women report pain during sexual activity, placing a significant financial burden on women and the healthcare system. Multiple medical treatments for dyspareunia are available to improve quality of life and decrease pain, however many are invasive, involving pharmacotherapy/hormone therapy/needle insertion/surgery, and are associated with significant morbidity. Low intensity shockwave therapy (LiSWT) is a non-invasive, non-pharmacologic, non-hormonal, non-surgical, low morbidity treatment strategy. FDA-cleared for pain amelioration in the

US as non-significant risk in humans, Urogold 100™ is an electrohydraulic shockwave device that generates energy levels such as 0.10-0.12 mJ/mm2 with a unique parabolic reflector. Objective: This chart review represents the first US-based treatment outcome study in women with vestibulodynia using Urogold 100™.

Methods: Patients presenting with vestibulodynia were offered the opportunity to receive LiSWT as a potential treatment for their genital pain disorder. As standard of care in our practice, patients completed the Female Sexual Function Index (FSFI), Sexual Distress Scale (SDS), vulvoscopy with photography, and cotton-tipped swab (Q-tip®) test at baseline. Vulvoscopic vulvar/vestibular photographs were scored for Vulvar/Vestibular Tissue Appearance (Vul/VestTA) (0 = normal appearance, 1 = minimal, 2 = moderate, 3 = severe concerns) for the vulva, vestibule and urethral meatus, with low scores associated with healthier tissue appearance. Cotton-tipped swab testing rated pain at the 1:00, 3:00, 5:00, 6:00, 7:00, 9:00 and 11:00 positions (0 = no pain, 1 = minimal, 2 = moderate, 3 = severe). The LiSWT protocol involved 6 treatment sessions, 3000 shocks each (1000 right/left lateral vestibule, and 1000 posterior vestibule), frequency 4/sec, membrane level 1. The energy varied from 0.10 – 0.12 mJ/mm^2, based on patient toleration. Patients underwent vulvoscopy with photography and cotton-tipped swab testing prior to each LiSWT, as is routine in our practice. At the end of treatment, patients recorded their treatment response by Patient Global Impression of Improvement (PGI-I), a scale of 1 – 7 with clinically relevant improvement expressed by scores of 1 – 3.

Results: To date data have been collected on 14 vestibulodynia patients, mean age 37 years (range 21 – 74). Mean baseline FSFI domain scores for desire, arousal, lubrication, orgasm, satisfaction and pain were: 2.6/6, 3.1/6, 3.4/6, 2.2/6, 2.6/6, and 1.6/6, respectively. Mean baseline Sexual Distress Scale score was 35.7/52, cotton-tipped swab test score was 2.6, and Vul/VestTA score was 2.5. Posttreatment, 9/14 (64%) of patients reported a PGI-I of 1 - 3. Post-treatment cotton-tipped swab testing score was diminished to 1.4 (consistent with mild pain). Post-treatment Vul/VestTA was 1.3 and vulvar/vestibular photographs revealed reduced vestibular pallor and erythema. No treatmentrelated side effects were reported. No patient experienced worsening of symptoms.

Conclusions: Vestibulodynia is a significant sexual health concern in women. Efforts to improve noninvasive, non-pharmacologic, non-hormonal, non-surgical, low morbidity treatment strategies should be encouraged. This chart review of LiSWT using Urogold 100™ is supporting the development of a prospective, sham-controlled clinical trial of LiSWT in women with vestibulodynia.

- **Efficacy of extracorporeal shockwave therapy in the treatment of postherpetic neuralgia: A pilot study** [60]

Established conventional treatments for postherpetic neuralgia (PHN) and postherpetic itch (PHI) are difficult and often disappointing. In this study, the authors investigated the effect and mechanisms of extracorporeal shockwave therapy (ESWT) on pain and itch associated with PHN and PHI.Thirteen patients, 50 to 80 years of age, with symptoms associated with PHN or PHI (duration of persistent pain >3 months) and complaints of pain or itch rated >4 on a numerical rating scale (NRS), were included. ESWT was administered using a shockwave device (Piezo Shockwave, Richard Wolf GmbH, Knittlingen, Germany) to skin areas affected by pain or itch. An energy flux density of 0.09 to 0.16 mJ/mm at a frequency of 5 Hz and 2000 impulses was administered at 3-day intervals for 6 sessions. The NRS, 5D-Itch Scale, and Patients Global Impression of Change (PGIC) scale were used to evaluate the efficacy of ESWT.NRS scores of pain and itch and 5D-Itch Scale scores decreased significantly compared with before treatment and at the end of the treatment sessions ($P < .0001$, $P = .001$, $P = .0002$, respectively). There was a statistically significant difference between PGIC scores, which were checked every 2 sessions ($P < .0001$). ESWT is a noninvasive modality that significantly reduced PHN-associated pain and itch.

❖ **Comparison of efficacy of corticosteroid injection versus extracorporeal shock wave therapy on inferior trigger points in the quadratus lumborum muscle: a randomized clinical trial** [61]

Background: In this study, we aimed to compare the efficacy of corticosteroid trigger point injection (TPI) versus extracorporeal shock wave therapy (ESWT) on inferior trigger points in the quadratus lumborum (QL) muscle.
Methods: In this single-blind randomized clinical trial, 54 low back pain patients with myofascial trigger points on QL muscle were investigated. Participants were randomly allocated into two groups with A and B pockets. Patients in group A underwent radial ESWT and received 5 treatment sessions (1 per week) and actually were not followed-up. However, patients in group B received corticosteroid TPI and received one session of corticosteroid treatment and followed-up for 4 weeks after injection. Oswestry Disability Index (ODI), visual analogue scale (VAS), pain pressure threshold (PPT) and short form (36) health survey (SF-36) were measured in both groups before, two weeks after and four weeks after intervention.
Results: The between group comparison indicated that corticosteroid TPI leaded to significant higher improvements of ODI (P-value< 0.01), VAS (P value< 0.001), and PPT (P-value = 0.001) scores compared to the ESWT group at two-week follow-up time-point. ESWT group recorded significant higher improvement of ODI (P-value< 0.01) and SF-36 (P-value< 0.001) compared to the corticosteroid TPI at 4th week post treatment evaluation. At four-week follow-up time-point, the patients in the ESWT group were 1.46 times more likely to achieve 30% reduction in VAS, 2.67 times more likely to achieve 30% reduction in ODI, and 2.30 times more likely to achieve 20% improvement in SF-36 compared to the participants in corticosteroid TPI group. These results refer to large effect size for all study outcomes in ESWT group (d = 4.72, d = 1.58, d = 5.48, and d = 7.47 for ODI, PPT, SF-36, and VAS, respectively).
Conclusion: Corticosteroid TPI was more effective compared to ESWT in short-term controlling of pain and disability caused by myofascial pain syndrome of QL muscle. However, after 4 weeks treatment, ESWT further improved the quality of life and disability and was related with more probability of achievement the minimal clinically important difference concerning pain, disability and quality of life and large effect size for all study outcomes in treated patients compared to corticosteroid TPI.

❖ **Case Series of Low Intensity Shock Wave Therapy for Men with Chronic Prostatitis / Chronic Pelvic Pain Syndrome** [62]

Introduction: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a heterogeneous syndrome that is often challenging to treat. Low Intensity Shock Wave (LiSW) has emerged as a potential therapy and several sham controlled studies have shown efficacy. We wished to study the efficacy and safety of LiSW in CP/CPPS patients with clinical phenotyping to better understand who may best respond.
Methods: Men were enrolled in this IRB approved study provided they had a diagnosis of CP/CPPS for at least 6 months and were able to return for weekly treatments. Those on multi-modal therapy continued other therapies as long as the dose was stable. LiSW was delivered with the Urogold 100 machine (Tissue Regeneration Technologies, Woodstock, GA) using the standard probe. There were 4 treatment sites, 2 on each side of the perineum at 500 shocks each for a total of 2000 shocks. Symptom severity was measured with the National Institute of Health Chronic Prostatitis Symptom Index (CPSI) at baseline and 1 month following the last treatment. Patients also self reported a General Response Assessment (GRA) ranging from 1 (significantly improved) to 5 (significantly worse). Patients were clinically phenotyped by the UPOINT system. Pre and post values were compared with the paired t test with significance set at p<0.05.
Results: 14 men enrolled with a mean age of 45.1 years (range 22-67) and median duration of 36 months (range 9-240). Men had a mean of 2.6 positive UPOINT domains (range 1-5) and all but 2 had pelvic floor tenderness (domain &[Prime]T&[Prime]). Total CPSI improved from 27.7 +/- 5.4 to 19.4 +/- 7.5 (p=0.003).

While the pain and quality of life scores improved significantly, there was no change in the urinary subscore. 9 patients (64.3%) had a >6 point drop in CPSI. By GRA, 7 patients said they were significantly improved, 2 was somewhat improved and 5 were unchanged. There were no significant differences in responders to non-responders for phenotype or symptom duration although responders had a higher starting pain score (14.0 vs 9.4, p=0.005) and both patients without pelvic floor spasm failed to improve.
Conclusions: LiSW with the Urogold 100 improved symptoms of CP/CPPS in the majority of patients. All responders had pelvic floor spasm, and shock wave therapy is well established in the treatment of pain from trigger points. While small numbers preclude meaningful subgroup analysis, there was no impact on urinary symptoms. In conclusion, once weekly low intensity shock wave lithotripsy improved the symptoms of CP/CPPS in the majority of patients without side effects.

❖ **Comparative study of shockwave therapy and low-level laser therapy effects in patients with myofascial pain syndrome of the trapezius** [63]

The objective of the study was to compare the effects of shockwave therapy and laser therapy on pain, neck functionality, and quality of life in patients with myofascial pain syndrome of the trapezius. 61 patients (> 18 years) were randomly allocated to two treatment groups: (1) 31 patients received soft laser therapy once daily in a 3-week period for a total of 15 sessions, (2) 30 patients received shockwave therapy once in a week for 3 weeks, totalling 3 treatments. Resting pain and pain tolerance were assessed by a 100 mm visual analogue scale; functional status and quality of life were measured by specific questionnaires (Neck Disability Index, SF-36) before and after the 3-week therapy and at the 15th week follow-up visit. All measured parameters improved significantly in both groups at week 3 and week 15. Comparing the two groups, patients receiving shockwave therapy demonstrated significantly better changes in pain tolerance (mean between-group differences at visit 1-0 = 14.911, 95% CI = 2.641-27.182, mean between-group differences at visit 2-0 = 17.190, 95% CI = 4.326-30.055 in the left trapezius), neck functionality (mean between-group differences at visit 1- 0 = 0.660, 95% CI = - 1.933 to 3.253, mean between-group differences at visit 2-0 = 1.072, 95% CI = - 2.110 to 4.254), and in all domains using SF-36 QoL questionnaire. The only parameter in which the laser group showed significantly higher benefits was at week 15 for resting pain (mean between-group differences at visit 2-0 = - 1.345, 95% CI = - 14.600 to 11.910). The results of our study point to a conclusion that both laser and shockwave therapy are effective in myofascial pain syndrome, though we found shockwave therapy to be somewhat more beneficial.

❖ **Effect of a Single Administration of Focused Extracorporeal Shock Wave in the Relief of Delayed-Onset Muscle Soreness: Results of a Partially Blinded Randomized Controlled Trial** [64]

Goethe-Universität Frankfurt am Main.
Objective: To examine the effects of a single administration of focused extracorporeal shock wave therapy on eccentric exercise-induced delayed-onset muscle soreness (DOMS).
Design: Three-arm randomized controlled study.
Setting: University research center.
Participants: Participants (N=46; 23 women) had a mean age of 29.0±3.0 years and a mean body mass index of 23.8±2.8kg/m^2.
Interventions: Participants were randomly allocated to verum- (energy flux density, .06-.09mJ/mm^2; pulse ratio per point, 200) or sham-focused extracorporeal shock wave therapy (no energy) at 7 equidistant points along the biceps muscle or no intervention.
Main outcome measures: The primary outcome was the difference in pain intensity. Secondary outcomes included maximum isometric voluntary force (MIVF), pressure pain threshold (PPT), and impairment in daily life.

Results: Despite descriptive clinically meaningful differences, mixed-effects analysis (group × time) of changes to baseline did not reveal significant differences in the reduction of pain intensity between groups ($F_{2,42}$=2.5, P=.094). MIVF was not significantly different between groups ($F_{2,43}$=1.9, P=.159). PTT ($F_{2,43}$=0.2, P=.854) and daily life impairment ($F_{2,42}$=1.4, P=.248) were not significantly decreased over time, and there were no differences between groups in the post hoc analysis.
Conclusions: DOMS is a common symptom in people participating in exercise, sports, or recreational physical activities. A single treatment with focused extracorporeal shock wave therapy causes clinically relevant effects in the relief of pain, increase in force, and improvement of pain-associated impairments of daily living. Still, results need to be cautiously interpreted because of the pilot character of this study. Focused extracorporeal shock wave therapy might present an option in the midterm recovery from DOMS (72h) and be an approach to enhance the return to play in athletes.

- **Efficacy of extracorporeal shockwave therapy (ESWT) for male chronic pelvic pain syndrome: a phase III, randomized, double blind controlled with placebo study** (Ramon et al., 2017)

Introduction: Chronic Prostatitis/ Chronic Pelvic Pain Syndrome (CP/CPPS) according to NIH is genitourinary pain or discomfort lasting 3 or more months with undetectable uropathogenic bacteria.
Material & Methods: Randomized, double blind, placebo controlled study has been conducted in 40 male patients who have had CPPS. Patients were randomly assigned to receive extracorporeal shock wave therapy (ESWT) or placebo. The study was conducted together by both Urology and Rehabilitation services. The primary outcome was to assess the efficacy of extracorporeal shock wave therapy for treatment of males CPPS.
Results: 38 patients were evaluated. ESWT group improved their pain relief statistically significantly compared to placebo group (11 +/- 3.15 vs 6.31 +/- 2.55, p<0.05). Also improved voiding quality as measured by IPSS score (11 +/- 2 vs 7.21 +/- 1.5, p<0.05). These results were maintained until 12 week. No AEs.
Discussion: At 4 and 12 weeks, patients who received ESWT experienced improvement in pain relief, quality of life, and voiding symptoms. In the literature the patients experienced the maximum relief of their symptomatology after 4 weeks of treatment, according to our results patients have achieved an improvement even better at 12 weeks. The results obtained are similar to those reported in the bibliography. Several studies in orthopedics, urology and cardiology have shown very low rate of AEs derived from ESWT.
Conclusion: It has been demonstrated ESWT is an effective and safe treatment for CPPS. Due to high prevalence of CPPS and none specific treatment, ESWT should be considered an effective and safe treatment alternative.

- **Extracorporeal Shockwave Therapy in Patients with Morton's Neuroma A Randomized, Placebo-Controlled Trial** [65]

Background: The aim of this study was to evaluate the efficacy of extracorporeal shockwave therapy (ESWT) for the treatment of Morton's neuroma by measuring changes in patient pain, function, and neuroma size.
Methods: Patients with Morton's neuroma were randomly assigned to either the ESWT group or the sham stimulation group. Outcome measures, including visual analog scale (VAS) and American Orthopaedic Foot and Ankle Society lesser toes (AOFAS) scores, were assessed at baseline and 1 and 4 weeks after treatment. The Johnson satisfaction test was also performed 1 and 4 weeks after treatment. The neuroma diameter was measured using ultrasonography at baseline and 4 weeks after treatment.

Results: Patients receiving ESWT exhibited significantly decreased VAS scores 1 and 4 weeks after treatment relative to baseline, and AOFAS scores were significantly improved 4 weeks after treatment relative to baseline. In the sham stimulation group, VAS and AOFAS scores showed no significant changes at any time after treatment. Neither group showed significant changes in Johnson satisfaction test results or neuroma diameter.
Conclusions: These results suggest that ESWT may reduce pain in patients with Morton's neuroma.

❖ **Dosage effects of extracorporeal shockwave therapy in early hip necrosis** [36]

Background: This study investigated the effects of different dosages of extracorporeal shockwave therapy (ESWT) in early osteonecrosis of the femoral head (ONFH).
Materials and methods: Thirty-three patients (42 hips) were randomly divided into three groups. Group A (10 patients with 16 hips) received 2000 impulses of ESWT at 24 Kv to the affected hip. Group B (11 patients with 14 hips) and Group C (12 patients with 12 hips) received 4000 and 6000 impulses of ESWT respectively. The evaluations included clinical assessment, radiographs, dynamic contrast-enhanced MRI for microcirculation (K^{trans}) and plasma volume (Vp), and blood tests for biomarker analysis (NO3, VEGF, BMP-2, osteocalcin, TNF-α, IL-6, substance P, CGRP, DKK-1 and IGF).
Results: Significant differences of pain and Harris hip scores were noticed between Group A and C in 6 months after ESWT (all $P < 0.05$). The pain score decreased, but not Harris hip score improved over the observation time period from 6 to 24 months. Total hip arthroplasty was performed in 3 patients (4 hips) in Group A, but none in Groups B and C. Group C showed significant changes in serum biomarkers for angiogenesis, osteogenesis, anti-inflammation, pain threshold and tissue regeneration between one week and one month after treatment (all $P < 0.05$). However, no significant changes in the infarction volume in image studies were noted in all groups (all $P > 0.05$). The post-treatment K^{trans} and Vp in the peri-necrotic areas of Group B and C were significantly greater than pre-treatment data (both $P < 0.05$).
Conclusions: High dosage ESWT is more effective in early stage ONFH. The systemic beneficial effects of ESWT may ultimately enhance angiogenesis with improvement of microcirculation of the peri-necrotic areas, that in turn, can improve subchondral bone remodeling and prevent femoral head collapse.

❖ **Extracorporeal Shock Wave Treatment: An Emerging Treatment Modality For Retracting Scars of The Hands** [66]

Department of Medical Sciences, Oral and Biotechnology, "G. D'Annunzio" University, Chieti, Italy.

Prolonged and abnormal scarring after trauma, burns and surgical procedures often results in a pathologic scar. We evaluated the efficacy of unfocused shock wave treatment, alone or in combination with manual therapy, on retracting scars on the hands. Scar appearance was assessed by means of the modified Vancouver Scar Scale; functional hand mobility was evaluated using a range-of-motion scale, whereas a visual analogue score was implemented for detecting any improvements in referred pain. Additionally, biopsy specimens were collected for clinico-pathologic correlation. For each active treatment group, statistically significant improvements in modified Vancouver Scar Scale were recorded as early as five treatment sessions and confirmed 2 wk after the last treatment session. Analogous results were observed when assessing pain and range of movement. Histopathological examination revealed significant increases in dermal fibroblasts in each active treatment group, as well as in neoangiogenetic response and type-I collagen concentration.

❖ **Efficacy of Extracorporeal Shock Wave Therapy for the Treatment of Chronic Pelvic Pain Syndrome: A Randomized, Controlled Trial** [17]

Objectives. To investigate the effectiveness of extracorporeal shock wave therapy (ESWT) for symptoms alleviation in chronic pelvic pain syndrome (CPPS). Materials and Methods. 40 patients with CPPS were randomly allocated into either the treatment or sham group. In the first group, patients were treated by ESWT once a week for 4 weeks by a defined protocol. In the sham group, the same protocol was applied but with the probe being turned off. The follow-up assessments were done at 1, 2, 3, and 12 weeks by Visual Analogue Scale (VAS) for pain and NIH-developed Chronic Prostatitis Symptom Index (NIH-CPSI). Results. Pain domain scores at follow-up points in both treatment and sham groups were reduced, more so in the treatment group, which were significant at weeks 2, 3, and 12. Urinary scores became significantly different at weeks 3 and 12. Also, quality of life (QOL) and total NIH-CPSI scores at all four follow-up time points reduced more significantly in the treatment group as compared to the sham group. Noticeably, at week 12 a slight deterioration in all variables was observed compared to the first 3 weeks of the treatment period. Conclusions. our findings confirmed ESWT therapy as a safe and effective method in CPPS in short term.

- **Extracorporeal shock wave therapy in myofascial pain syndrome of upper trapezius** [67]

Objective: To evaluate the effect of extracorporeal shock wave therapy (ESWT) in myofascial pain syndrome of upper trapezius with visual analogue scale (VAS) and pressure threshold by digital algometer.
Method: Twenty-two patients diagnosed with myofascial pain syndrome in upper trapezius were selected. They were assigned to treatment and standard care (control) groups balanced by age and sex, with eleven subjects in each group. The treated group had done four sessions of ESWT (0.056 mJ/mm(2), 1,000 impulses, semiweekly) while the control group was treated by the same protocol but with different energy levels applied, 0.001 mJ/mm(2). The VAS and pressure threshold were measured twice: before and after last therapy. We evaluated VAS of patients and measured the pressure threshold by using algometer.
Results: There were two withdrawals and the remaining 20 patients were three men and 17 women. Age was distributed with 11 patients in their twenties and 9 over 30 years old. There was no significant difference of age, sex, pre-VAS and pre-pressure threshold between 2 groups ($p>0.05$) found. The VAS significantly decreased from 4.91±1.76 to 2.27±1.27 in the treated group ($p<0.01$). The control group did not show any significant changes of VAS score. The pressure threshold significantly increased from 40.4±9.94 N to 61.2±12.16 N in the treated group ($p<0.05$), but there was no significant change in the control group.
Conclusion: ESWT in myofascial pain syndrome of upper trapezius is effective to relieve pain after four times therapies in two weeks. But further study will be required with more patients, a broader age range and more males.

- **Extracorporeal shock wave treatment for non-inflammatory chronic pelvic pain syndrome: a prospective, randomized and sham-controlled study** [68]

Background: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical syndrome characterized by pain in the perineum, pelvis, suprapubic area, or external genitalia and variable degrees of voiding and ejaculatory disturbance. The analgesic effect of extracorporeal shock wave treatment (ESWT) was an interesting phenomenon with an unclear mechanism discovered by chance in the applications for urolithiasis, on which ESWT has become an increasingly popular therapeutic approach as an alternative option for the treatment of a number of soft tissue complaints. In this study, we aimed to evaluate the feasibility and efficacy of ESWT in non-inflammatory (IIIB) CP/CPPS.
Methods: Men diagnosed with IIIB CP/CPPS were randomized to either ESWT (group 1, n = 40) or the control (group 2, n = 40). Group 1 received 20 000 shock wave impulses in 10 sessions over a two-week

period, whereas group 2 received only a sham procedure. The total scores and sub-domain scores of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) for both groups were assessed at baseline, mid-treatment, end-point, and 4-week and 12-week follow-up visits.
Results: The mean total NIH-CPSI score of group 1 was significantly decreased from baseline at all post-treatment time points ($P < 0.01$ for all). Decreases in pain domain and quality of life (QOL) scores were also significant. In group 2, no significant decreases of total NIH-CPSI score and pain domain score were found at all post-treatment time points. At the end-point of treatment, 71.1% of group 1 exhibited perceptible improvement in total NIH-CPSI compared with 27.0% of group 2 ($P < 0.001$); additionally, 28.9% of group 1 exhibited clinically significant improvement compared with 10.8% of group 2 ($P < 0.01$). Moreover, a greater number of patients in group 1 at 4-week and 12-week follow-up were rated as responders (perceptible and clinically significant response) compared with group 2.

- **Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study** [18]

Background: There is no sufficiently validated therapy for chronic pelvic pain syndrome (CPPS).
Objective: To investigate the effects of extracorporeal shock wave therapy (ESWT) in 60 patients suffering from CPPS.
Design, setting, and participants: Sixty patients suffering from CPPS for at least 3 mo were investigated in two groups. Both groups were treated four times (once per week), each by 3000 impulses; group 2 was performed as a sham procedure. The investigation was designed as a placebo-controlled, prospectively randomised, double-blind phase 2 study. Standardised follow-up was performed 1, 4, and 12 wk after ESWT.
Interventions: Low-energy-density ESWT was performed using a perineal approach without anaesthesia. In the placebo group, the same setting was used without shock wave energy transmission.
Measurements: ESWT effects on pain, quality of life (QoL), erectile function (EF), and micturition were evaluated. The parameters were investigated using validated questionnaires (National Institutes of Health Chronic Prostatitis Symptom Index [NIH-CPSI], International Prostate Symptom Score [IPSS], International Index of Erectile Function [IIEF]) and the Visual Analog Scale (VAS) for pain evaluation.
Results and limitations: All patients completed outpatient treatments and follow-ups without any problems. All 30 patients in the verum group showed statistically (highly) significant improvement of pain, QoL, and voiding conditions following ESWT in comparison to the placebo group, which experienced a continuous deterioration of the same parameters during the follow-up period. Perineal ESWT was easy and safe to perform without anaesthesia or any side-effects.
Conclusions: This is the first prospectively randomised, double-blind study to reveal perineal ESWT as a therapy option for CPPS with statistically significant effects in comparison to placebo. ESWT may in particular be interesting because of its easy and inexpensive application, the lack of any side-effects, and the potential for repetition of the treatment at any time.

- **Application of local anesthesia inhibits effects of low-energy extracorporeal shock wave treatment (ESWT) on nociceptors** [69]

Objective: Clinical studies of extracorporeal shock wave therapy (ESWT) provided conflicting results depending on the use of local anesthesia (LA).
Design: The present study investigated whether the biological effects of ESWT differ between application with and without LA.
Setting and patients: In 20 healthy subjects, ESWT was applied to the ventral surface of forearm skin, either after topical lidocaine pretreatment or without on the corresponding contralateral side.

Measures: During and after ESWT ongoing pain, axon-reflex vasodilation (laser Doppler imaging), thresholds for pinprick, and blunt pressure were recorded.
Results: The results indicate that increasing ESWT energy flux density led to increasing pain ($P < 0.001$). LA reduced ESWT-related pain ($P < 0.02$) and in parallel inhibited local axon-reflex vasodilation ($P < 0.001$). In addition, LA prevented ESWT-related drop in pressure pain threshold ($P < 0.001$).
Conclusion: This study provided evidence that ESWT dose-dependently activates and sensitizes primary afferent nociceptive C-fibers, and that both activation and sensitization were prevented if LA was applied locally. These results suggest that LA substantially alters the biological responses of ESWT.

❖ A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease [70]

Background: Extracorporeal shock wave therapy (ESWT) is a conservative therapy for patients with Peyronie's disease (PD).
Objective: To investigate the effects of ESWT in patients with PD.
Design, setting, and participants: One hundred patients with a history of PD not >12 mo who had not had previous PD-related treatments were enrolled in a prospective, randomized, double-blind, placebo-controlled study. Patients were randomly allocated to either ESWT (n=50) or placebo (n=50). Erectile function (EF), pain during erection, plaque size, penile curvature, and quality of life (QoL) were assessed at baseline, at 12 wk, and at 24 wk follow-up.
Intervention: Four weekly treatment sessions were administered. Each ESWT session consisted of 2000 focused shock waves. For the placebo group, a nonfunctioning transducer was employed.
Measurements: EF was evaluated with the shortened version of the International Index of Erectile Function (IIEF-5), pain was evaluated with a visual analog scale (VAS; 0-10), plaque size was measured in cm(2), and penile curvature was measured in degrees.
Results and limitations: After 12 wk, mean VAS score, mean IIEF-5 score, and mean QoL score ameliorated significantly in patients receiving ESWT. Mean plaque size and mean curvature degree were unchanged in the ESWT group, while a slight increase was reported in the placebo group (p-value not significant vs baseline). After 24 wk, mean IIEF-5 score and mean QoL score were stable in the ESWT group, while mean VAS score was significantly lower when compared with baseline in both groups. Interestingly, after 24 wk, mean plaque size and mean curvature degree were significantly higher in the placebo group when compared with both baseline and ESWT values. The main limitations were that the QoL questionnaire was not validated, ED was not etiologically characterized, and inclusion criteria were restricted.

5.3. Expert Reviews

❖ **Extracorporeal shock wave therapy mechanisms in musculoskeletal regenerative medicine** [14]

Extracorporeal shockwave therapy (ESWT) is a popular non-invasive therapeutic modality in the medical field for the treatment of numerous musculoskeletal disorders. This technique first emerged around the 1980s as extracorporeal shockwave lithotripsy and has been studied since then for its application towards orthopedics and traumatology. ESWT works by the emission of acoustic waves (shockwaves) that carry energy and can propagate through tissues. Shockwaves can generate interstitial and extracellular responses, producing many beneficial effects such as: pain relief, vascularization, protein biosynthesis, cell proliferation, neuro and chondroprotection, and destruction of calcium deposits in musculoskeletal structures. The combination of these effects can lead to tissue regeneration and significant alleviation of pain, improving functional outcomes in injured tissue. Considering these facts, ESWT shows great

potential as a useful regenerative medicine technique for the treatment of numerous musculoskeletal injuries.

❖ **Molecular mechanism of action of low-intensity extracorporeal shockwave therapy for regenerating penile and peripheral nerves** [71]

Sufficient functional repair of damaged peripheral nerves is a big clinical challenge in terms of long-lasting morbidity, disability, and economic costs. Nerve damage after radical prostatectomy is the most common cause of erectile dysfunction (ED). In recent years, low-intensity extracorporeal shockwave therapy (Li-ESWT) has been explored to improve the outcomes of peripheral nerve repair and regeneration. Research indicated that application of Li-ESWT after nerve surgery promoted nerve regeneration and improved the functional outcomes, underlined the mechanisms related to increase of neurotrophic factors, Schwann cells activation, and cellular signaling activation for cell activation and mitosis induced by Li-ESWT. We searched PubMed for articles related to research on these topics in both in vitro and in vivo animal models and found numerous studies suggesting that the application Li-ESWT could be a novel treatment for ED induced by nerve injury and other disease related to nerve injury.

❖ **Cellular Signaling Pathways Modulated by Low-intensity Extracorporeal Shock Wave Therapy** [72]

Low-intensity extracorporeal shock wave therapy (Li-ESWT) is a form of energy transfer that is of lower intensity (<0.2 mJ/mm^2) relative to traditional Extracorporeal Shock Wave Lithotripsy (ESWL) used for management of urinary stones. At this intensity and at appropriate dosing energy transfer is thought to induce beneficial effects in human tissues. The proposed therapeutic mechanisms of action for Li-ESWT include neovascularization, tissue regeneration, and reduction of inflammation. These effects are thought to be mediated by enhanced expression of vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen. Upregulation of chemoattractant factors and recruitment/activation of stem/progenitor cells may also play a role. Li-ESWT has been studied for management of musculoskeletal disease, ischemic cardiovascular disorders, Peyronie's Disease, and more recently erectile dysfunction (ED). The underlying mechanism of Li-ESWT for treatment of ED is incompletely understood. We summarize the current evidence basis by which Li-ESWT is thought to enhance penile hemodynamics with an intention of outlining the fundamental mechanisms by which this therapy may help manage ED.

❖ **Effect of Shockwave Treatment for Management of Upper and Lower Extremity Musculoskeletal Conditions: A Narrative Review** [73]

Extracorporeal shockwave therapy (ESWT) is a technology that was first introduced into clinical practice in 1982 for urologic conditions. Subsequent clinical applications in musculoskeletal conditions have been described in treatment of plantar fasciopathy, both upper and lower extremity tendinopathies, greater trochanteric pain syndrome, medial tibial stress syndrome, management of nonunion fractures, and joint disease including avascular necrosis. The aim of this review is to summarize the current understanding of treatment of musculoskeletal conditions with ESWT, accounting for differences in treatment protocol and energy levels. Complications from ESWT are rare but include 2 reported cases of injury to bone and Achilles tendon rupture in older adults using focused shockwave. Collectively, studies suggest ESWT is generally well-tolerated treatment strategy for multiple musculoskeletal conditions commonly seen in clinical practice.

❖ **CLINICAL APPLICATION OF SHOCK WAVE THERAPY IN MUSCULOSKELETAL DISORDERS: PART I** [16]

The shock wave has been widely recognized in literature as a biological regulator; therefore we carried out a review on the activity performed by shock waves on the bone-myofascial tissue system. To date, the application of Shock Wave Therapy (SWT) in musculoskeletal disorders has been primarily used in the treatment of tendinopathies (proximal plantar fasciopathy, lateral elbow tendinopathy, calcific tendinopathy of the shoulder, and patellar tendinopathy, etc.) and bone defects (delayed- and non-union of bone fractures, avascular necrosis of femoral head, etc.). Although the mechanism of their therapeutic effects is still unknown, the majority of published papers have shown positive and beneficial effects of using SWT as a treatment for musculoskeletal disorders, with a success rate ranging from 65 to 91%, while the complications are low or negligible. The purpose of this paper is to inform the reader about the published data on the clinical application of SWT in the treatment of musculoskeletal disorders. In this paper, with the help of a literature review, indications and success rates for SWT in the treatment of musculoskeletal disorders are outlined, while adequate SWT parameters (e.g., rate of impulses, energy flux density, etc.) are defined according to the present state of knowledge. Given the abundance of the argument, it seems appropriate to subdivide the review into two parts, the first concerning the evidence of Extracorporeal Shock Wave Therapy (ESWT) on bone disorders, the second concerning findings on tendon and muscle treatment.

❖ **Clinical application of shock wave therapy in musculoskeletal disorders: part II related to myofascial and nerve apparatus** [74]

Shock waves have been widely recognized in literature as a biological regulator; accordingly we carried out a review on the effect of shock waves on the mesenchymal cells in their various expressions: bone, muscle, ligament and tendon tissue. To date, the application of Shock Wave Therapy (SWT) in musculoskeletal disorders has been primarily used in the treatment of tendinopathies (proximal plantar fasciopathy, lateral elbow tendinopathy, calcific tendinopathy of the shoulder, and patellar tendinopathy, etc.) and bone defects (delayed and non-union of bone fractures, avascular necrosis of femoral head, etc.). Although the mechanism of their therapeutic effects is still unknown, the majority of published papers have shown the positive and beneficial effects of using SWT as a treatment for musculoskeletal disorders, with a success rate ranging from 65% to 91%, while the complications are low or negligible. The purpose of this paper is to present the published data on the clinical application of SWT in the treatment of myofascial and nerve disorders. With the help of the relevant literature, in this paper we outline the indications and success rates of SWT, as well as the adequate SWT parameters (e.g., rate of impulses, energy flux density) defined according to the present state of knowledge.

❖ **Update on the efficacy of extracorporeal shockwave treatment for myofascial pain syndrome and fibromyalgia** [75]

Chronic muscle pain syndrome is one of the main causes of musculoskeletal pathologies requiring treatment. Many terms have been used in the past to describe painful muscular syndromes in the absence of evident local nociception such as myogelosis, muscle hardening, myalgia, muscular rheumatism, fibrositis or myofascial trigger point with or without referred pain. If it persists over six months or more, it often becomes therapy resistant and frequently results in chronic generalized pain, characterized by a high degree of subjective suffering. Myofascial pain syndrome (MPS) is defined as a series of sensory, motor, and autonomic symptoms caused by a stiffness of the muscle, caused by hyperirritable nodules in musculoskeletal fibers, known as myofascial trigger points (MTP), and fascial constrictions. Fibromyalgia (FM) is a chronic condition that involves both central and peripheral sensitization and for which no curative treatment is available at the present time. Fibromyalgia shares some of the features of MPS, such

as hyperirritability. Many treatments options have been described for muscle pain syndrome, with differing evidence of efficacy. Extracorporeal Shockwave Treatment (ESWT) offers a new and promising treatment for muscular disorders. We will review the existing bibliography on the evidence of the efficacy of ESWT for MPS, paying particular attention to MTP (Myofascial Trigger Point) and Fibromyalgia (FM).

- **Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action** [76]

Shock waves (SW), defined as a sequence of single sonic pulses characterised by high peak pressure (100 MPa), a fast rise in pressure (< 10 ns) and a short lifecycle (10 micros), are conveyed by an appropriate generator to a specific target area at an energy density ranging from 0.03 to 0.11 mJ/mm(2). Extracorporeal SW (ESW) therapy was first used on patients in 1980 to break up kidney stones. During the last ten years, this technique has been successfully employed in orthopaedic diseases such as pseudoarthosis, tendinitis, calcarea of the shoulder, epicondylitis, plantar fasciitis and several inflammatory tendon diseases. In particular, treatment of the tendon and muscle tissues was found to induce a long-time tissue regeneration effect in addition to having a more immediate anthalgic and anti-inflammatory outcome. In keeping with this, an increase in neoangiogenesis in the tendons of dogs was observed after 4-8 weeks of ESW treatment. Furthermore, clinical observations indicate an immediate increase in blood flow around the treated area. Nevertheless, the biochemical mechanisms underlying these effects have yet to be fully elucidated. In the present review, we briefly detail the physical properties of ESW and clinical cases treated with this therapy. We then go on to describe the possible molecular mechanism that triggers the anti-inflammatory action of ESW, focusing on the possibility that ESW may modulate endogenous nitric oxide (NO) production either under normal or inflammatory conditions. Data on the rapid enhancement of endothelial NO synthase (eNOS) activity in ESW-treated cells suggest that increased NO levels and the subsequent suppression of NF-kappaB activation may account, at least in part, for the clinically beneficial action on tissue inflammation.

- **A neural model for chronic pain and pain relief by extracorporeal shock wave treatment** [19]

The paper develops a new theory of chronic pain and pain relief by extracorporeal shock wave treatment. Chronic pain without underlying anatomical disorder is looked at as a pathological control function of memory. Conditioned reflexes are considered to be engraved memory traces linking sensory input of afferent signals with motor response of efferent signals. This feature can be described by associative memory functions of the nervous system. Some conditioned reflexes may cause inappropriate or pathological reactions. Consequently, a circulus vitiosus of pain sensation and muscle and/or vessel contraction is generated when pain becomes chronic (pain spiral). The key feature is a dedicated engram responsible for a pathological (painful) reaction. The pain memory may be explained by the concept of a holographic memory model published by several authors. According to this model it is shown how nervous systems may generate and recall memory contents. The paper shows how extracorporeal shock wave treatment may reorganize pathologic memory traces, thus giving cause to real and permanent pain relief. In a generalized manner, the idea of associative memory functions may help in the understanding of conditioning as a learning process and explain extracorporeal shock wave application as an efficient treatment concept for chronic pain. This concept may open the door for new treatment approaches to chronic pain and several other disorders of the nervous system.

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