TRT Tissue Regeneration Technologies

TRT SoftWave® Therapy

Tissue Activation and Regeneration in Sports Medicine and Bone Pathologies

aossm

ANNUAL MEETING 2019

JOHN B. HYNES VETERANS MEMORIAL CONVENTION CENTER
BOSTON, MA • JULY 11 – 14, 2019

Content Outline

- Shock Wave Definition
- Shock Wave Generation
- Difference between Focused Shock Wave and Radial Pressure Wave
- Physical Mechanisms
- Biological Effects
- TRT SoftWave® Technology
- Application Areas - Overview
- SoftWave ® Therapy – Bone Augmentation and Stem Cell Stimulation
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- SoftWave ® Therapy – Therapeutic Effects
- SoftWave ® Therapy – Conclusion
- SoftWave ® Therapy – References
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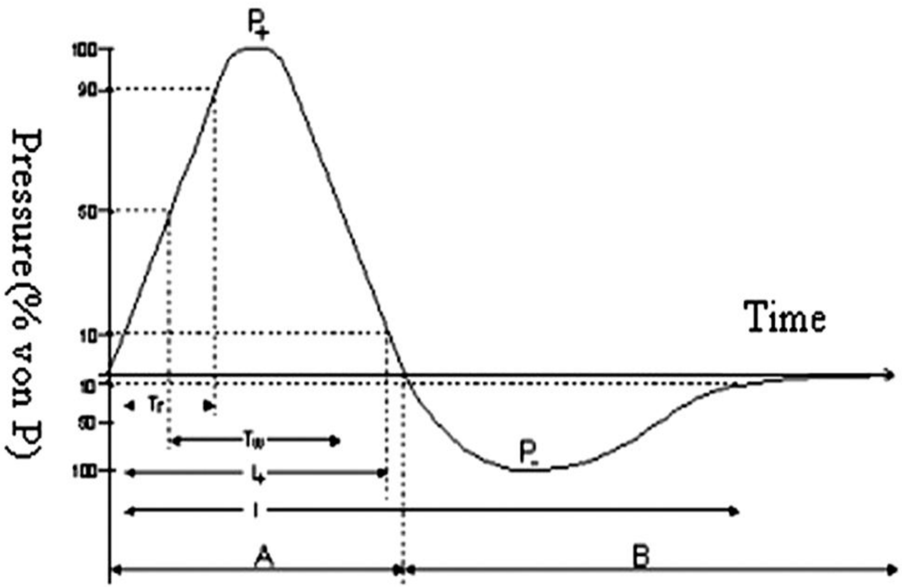
Shock Wave Definition

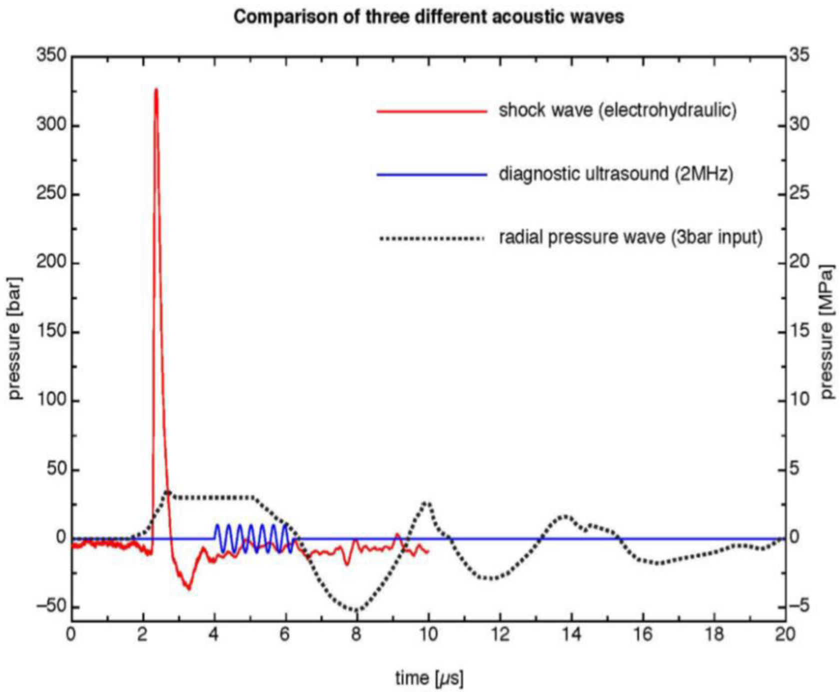


Characteristics:

1. Extremely rapid rise of the curve
2. Very high pressure
3. Low negative wave compared to the very high peak pressure

Fig. 1: Illustration of a shock wave according to IEC 61846. Shock wave pressure is shown as a function of time. A, first portion of the shock wave with positive pressure; B, second portion of the shock wave with negative pressure; P+, positive peak pressure; P-, negative peak pressure; Tr, rise time; Tw, impulse width; I+, standard time interval to calculate the shock wave's so-called "positive energy"; I, standard time interval to calculate the shock wave's so-called overall energy.

Shock Wave Definition



Source:
electrohydraulic shock wave: MTS Europe GmbH, measurement orthogold100, focused applicator
diagnostic ultrasound: sine wave, calculated with 1 MPa peak pressure at 2MHz
radial pressure wave: R. O. Cleveland, P. V. Chitnis, and S. R. McClure. Acoustic field of a ballistic shock wave therapy device. Ultrasound Med Biol, 33(8):1327–1335, 2007, Figure 6a

Parameters currently in use:

•Positive pressure	MPA
•-6 dB focus	mm
•5 MPa focus	mm
•Positive energy flux density (EFD+)	mJ / mm^2
•Total EFD	mJ / mm^2
•Positive energy of the -6 dB focus	mJ
•Positive energy of the 5 Mpa focus	mJ
•Positive energy of the 5 mm focus	mJ
•Total energy of the 5 mm focus	mJ

Fig. 2: Shock waves are mechanical pressure impulses which propagate in the medium in a wave-like manner.
(digest 2018)

Shock Wave Generation

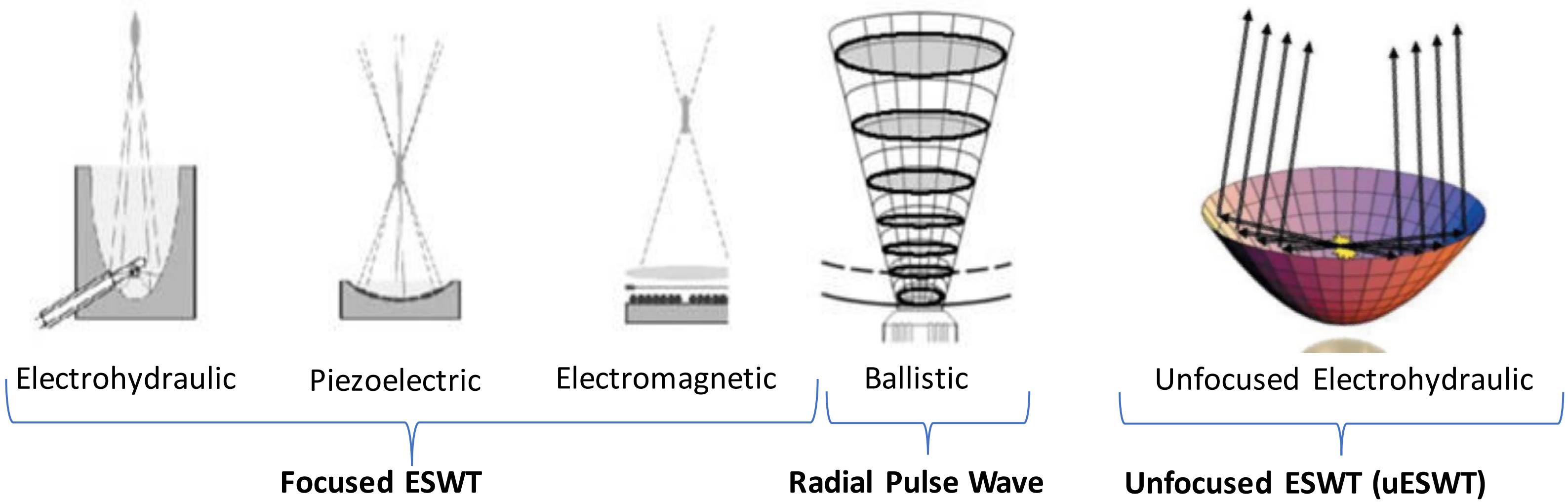
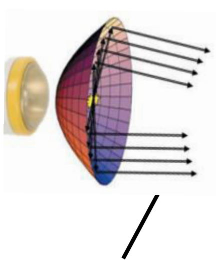


Fig. 3: Focused shock waves can be generated with electrohydraulic, piezoelectric and electromagnetic techniques. Ballistic techniques produce radial pressure waves (not shock waves). Electrohydraulic is the only method that produces a true shock wave at the source. Others only achieve a shock wave at the focal point. (https://burningscience.wordpress.com)

uESWT delivers a far larger zone of energy, than Focused, and reaches 4x the depth of radial pulse wave devices. uESWT is nontraumatic, so over shooting targets is not an issue.

Differences between Unfocused Shock Waves and Radial Pressure Waves During Application

TRT Unfocused



Energy spread over large area	Minimal negative pressure	Large therapeutic zone	Greater depth of prenetration
Significantly Reduced Pain	NO side-effects	Fewer treatments Better outcomes	Wide treatment range

Radial Wave

Energy spreads radially	High negative pressure, highest energy superficial	Reduction of energy due to propagation attenuation	Low penetration depth
Pain numbing cream required	Risk of hematoma	More treatments	Small treatment range, only superficial

Physical Mechanisms

Acoustic impedance:

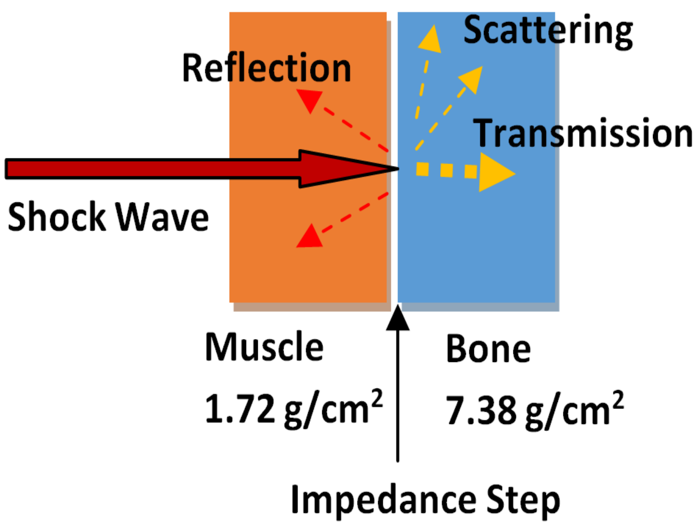


Fig. 5: Energy is released at interfaces, at those places where the waves from one medium meet another medium. (digest 2018.)

Physical phenomena at the interfaces:

•Transmission (transverse wave, longitudinal wave)

•(Partial) reflection

•Diffraction and / or deflection, scattering

•Wave velocity x density of the medium = acoustic impedance

•Pressure / tension wave, shear forces

Physical Mechanisms

Cavitation:

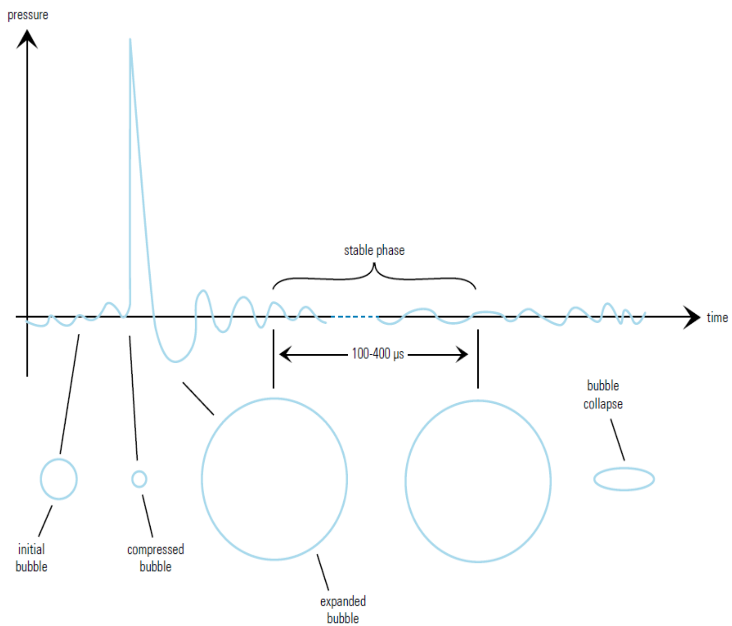


Fig. 6: Life of a cavitation bubble in water, before and after shock wave passage. (Loske, Achim, 2013, Shock Wave Physics for Urologists.)

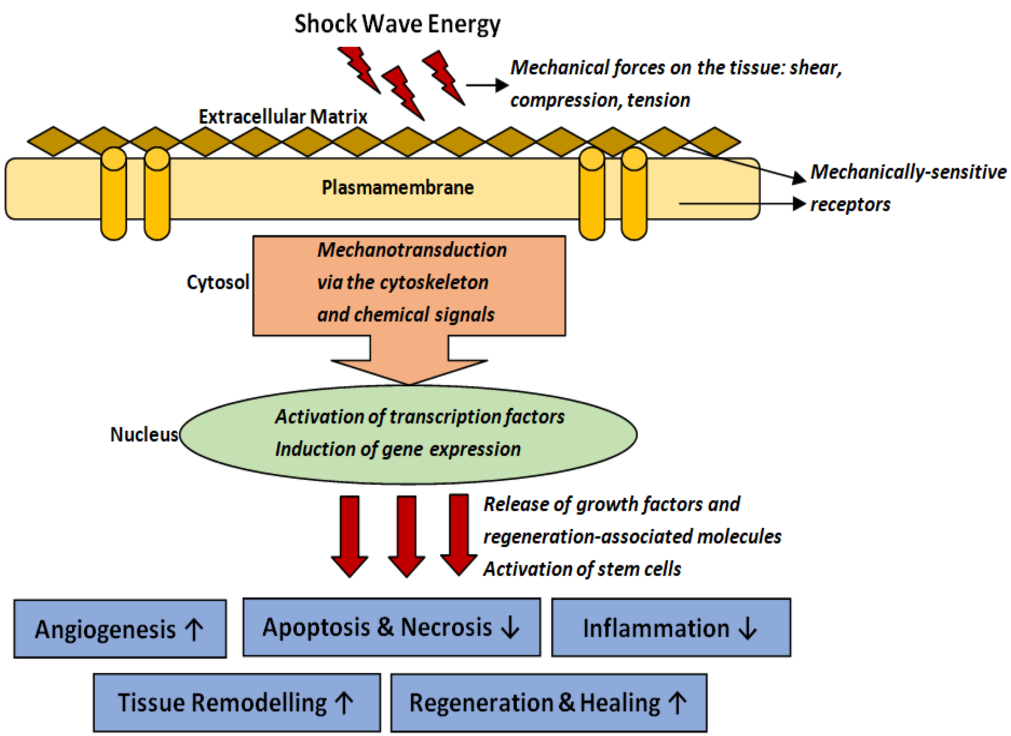
•Cavitation (lat. cavitare "hollow out") is the formation and dissolution of vapour-filled cavities (vapour bubbles) in liquids.

•Due to the extreme pressure differences, bubbles form in the medium, the bubbles collapse and the released energy generates further shock waves (jet streams) and photons or free radicals.

•This phenomenon can be proven in experiments, but today it is not possible to say how necessary cavitation is in order to produce a biological effect.

Biological Effects

Mechanotransduction:



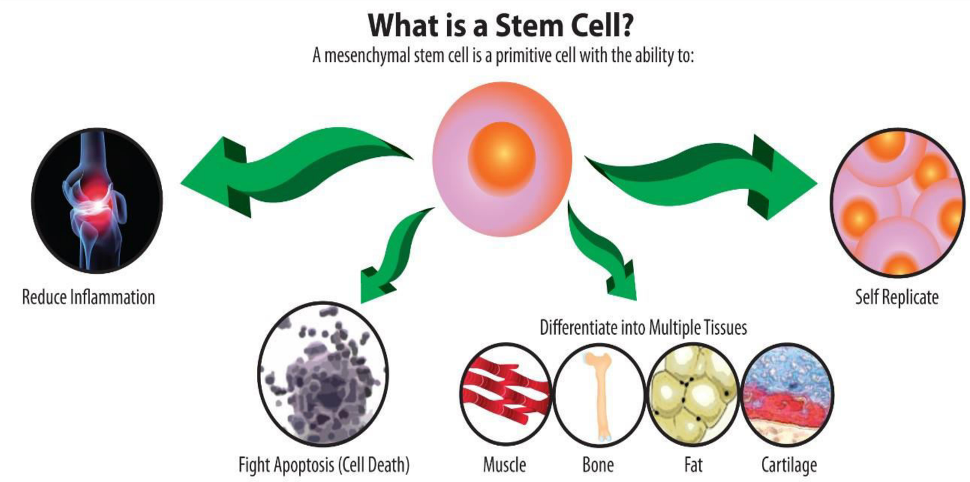
- The physical shaking of the tissue by the shock waves leads to a mechanotransduction; the conversion of mechanical signals (e. g. shear, compression, tension) into electrical or chemical signals responses in the tissue.
- The stimulation of mechanically sensitive molecules, the mechanoreceptors at the plasma membrane (e. g. ion channels, components of the extracellular matrix and the cytosketon) leads to cellular responses.
- Following the stimulation of the cell nucleus via the excited cytoskeleton leads to an enzymatic tissue response and the expression / release of transcription factors, cytokines, growth factors etc.
- A cascade of regeneration events is initiated and the metabolism, migration, proliferation and differentiation of stem / progenitor cells is initiated.
- This leads to enhanced angiogenesis and neovascularisation, reduced cell apoptosis and tissue necrosis, modulation of inflammation and finally to improved tissue remodeling and regeneration.

Biological Effects

Tissue regeneration:

- Capacity of the body to replace damaged or lost parts.
- Regenerative medicine: Recapitulates and stimulates the molecular events that allow stem cells to repair the damaged tissue / organ.
- **TRT SoftWave® Therapy:**
- ✓ Induces self-healing - where the body uses its own system to rebuild tissues.
- ✓ Focuses on cures of treatments for complex, often chronic, diseases.

→ ***Tuning stem cell fate!***



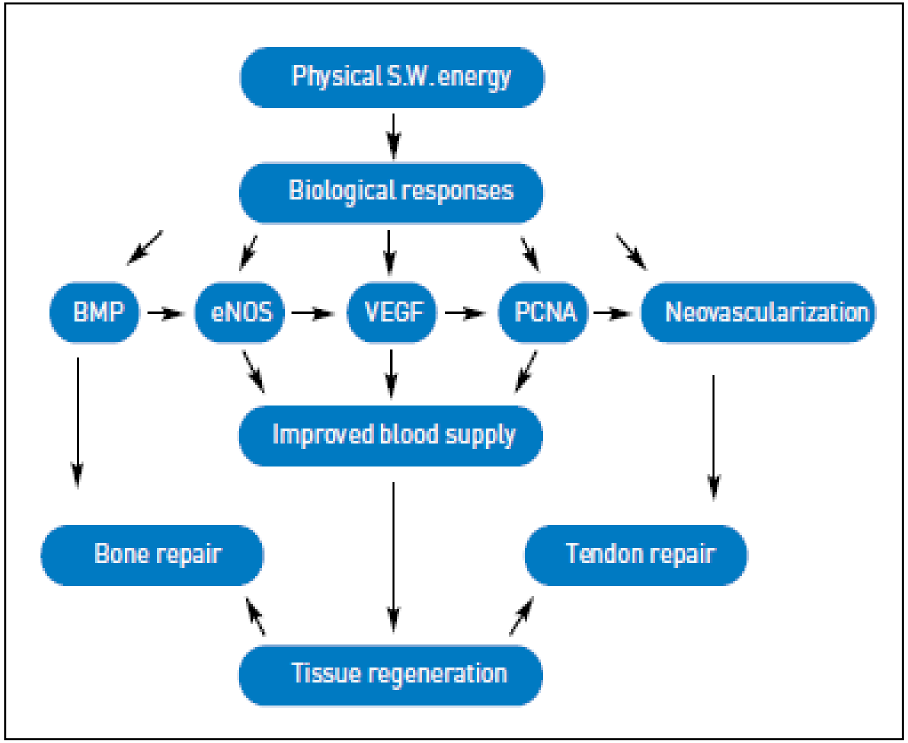
https://www.bisturmed.si/en/prp-theraphy/stem-cells

Biological Effects

Tissue regeneration:

Expression of regeneration-associated molecules:

- VEGF (vascular endothelial growth factor)
- eNOS (endothelial nitric oxide synthase)
- BMP (bone morphogenetic protein)
- PCNA (proliferating cell nuclear antigen)
- SDF-1 (stromal-derived factor 1)
- IGF-1 (insulin-like growth factor 1)
- FGF-ß (fibroblast growth factor ß)
- TGF-ß (transforming growth factor ß)
- TNF-α (tumor necrose factor α)
- ATP (adenosine triphosphate)
- Interleukins (IL-1, IL-6, IL-8, IL-10)
- ...



Wang et al (2006): Biological mechanism of musculoskeletal shockwaves. 9th Congress of the International Society for Medical Shockwave Treatment.

TRT Tissue Regeneration Technologies

TRT SoftWave® Technology

orthogold100®

Unfocused applicator OP155

Application Areas - Overview

Orthopaedics / Physiotherapy & Rehabilitation / Sports Medicine
Traumatology & Bone Repair / Musculoskeletal & Joint Diseases / Nerve Regeneration

Approved standard indications:

Chronic Tendinopathies
- Calcifying tendinopathy of the shoulder
- Lateral epicondylopathy tennis elbow
- Greater trochanter pain syndrome
- Patellar tendinopathy
- Achilles tendinopathy
- Plantar fasciitis, heel spur

Bone Pathologies
- Delayed bone healing
- Bone Non-Union (pseudarthrose)
- Stress fracture
- Avascular bone necrosis
- Osteochondritis Dissecans (OCD)

Skin Pathologies
- Delayed or non-healing wounds
- Skin ulcers
- Non-circumferential burn wounds

Common empirically-tested clinical uses:

Tendinopathies
- Rotator cuff tendinopathy
- Medial epicondylopathy of the elbow
- Adductor tendinopathy syndrome
- Pes-Anserinus tendinopathy syndrome
- Peroneal tendinopathy
- Foot and ankle tendinopathies

Bone Pathologies
- Bone marrow edema
- Osgood Schlatter disease
- Tibial stress syndrome (shin splint)

Muscle Pathologies
- Myofascial Syndrome
- Muscle sprain without discontinuity

Skin Pathologies
- Cellulite
- Lymphedema

Exceptional indications – expert indications:

Musculoskeletal pathologies
- Osteoarthritis
- Dupuytren disease
- Plantar fibromatosis (Ledderhose disease)
- De Quervain disease & Trigger finger
- Foot and ankle tendinopathies

Neurological Pathologies
- Spasticity
- Polyneuropathy
- Carpal Tunnel Syndrome

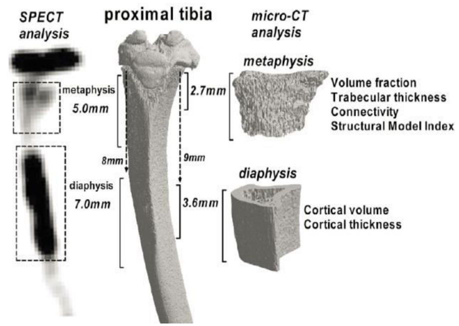
Urologic Pathologies
- Pelvic chronic pain syndrome
- Erectile dysfunction
- Peyronie disease

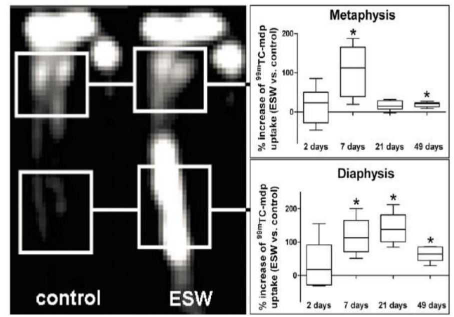
Experimental
- Heart Muscle Ischemia
- Peripheral nerve lesions
- Pathologies of the spinal cord and brain
- Osteoporosis

SoftWave® Therapy – Bone Augmentation

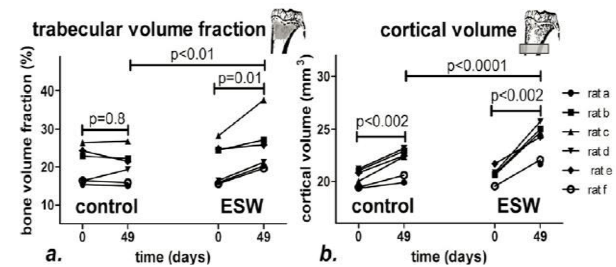
SoftWaves® promote bone formation

Van der Jagst et al., 2011, „Unfocused Extracorporeal Shock Waves Induce Anabolic Effects in Rat Bone“

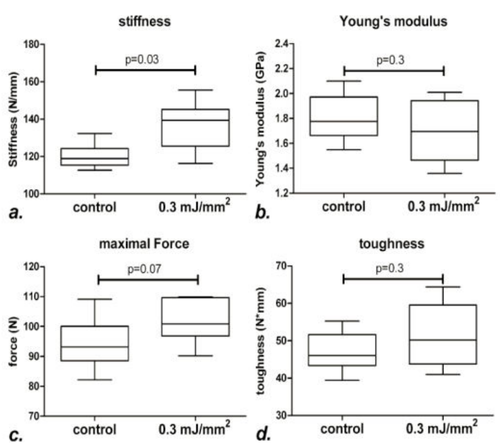




Increase of new bone formation in ESWT treated tibiae relative to the control.

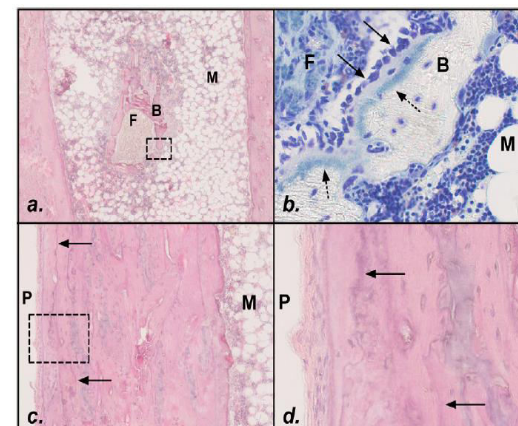


Microarchitectural bone changes.



Mechanical Testing. The stiffness of the treated tibiae was significantly higher than that of untreated control tibiae.

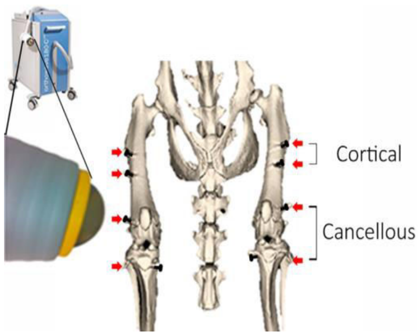
Histological examination. Bone (B), bone marrow (M), fibrous tissue (F). Active bone formation with active osteoblasts (solid arrows) and osteoid (dashed arrows) at the surface of mature bone that contains osteocytes.



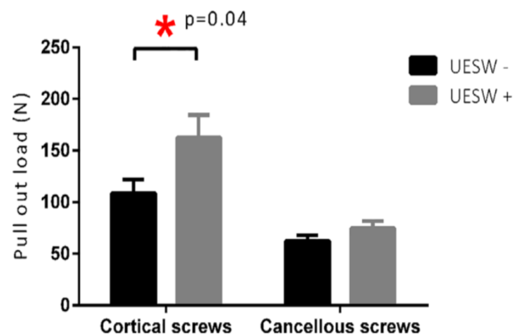
SoftWave® Therapy – Bone Augmentation

SoftWaves® promote bone formation

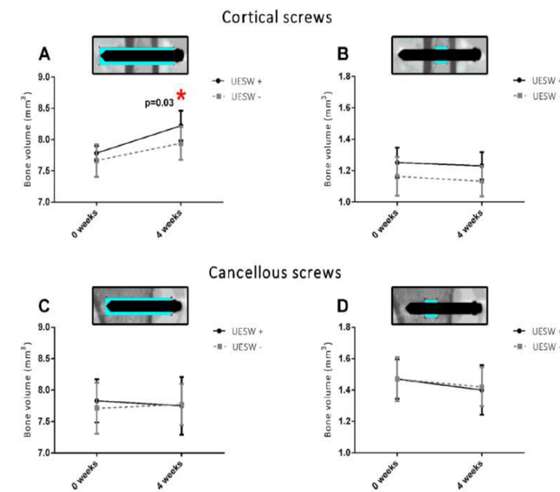
Koolen et al., 2017, „Optimization of Screw Fixation in Rat Bone With Extracorporeal Shock Waves“



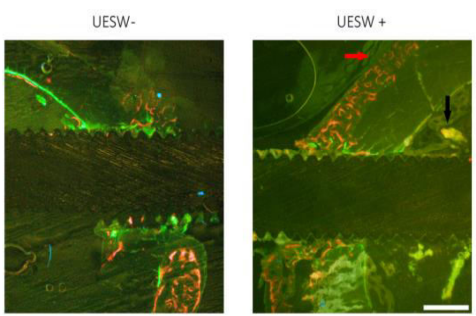
Experimental set-up. Positions of the implanted screws



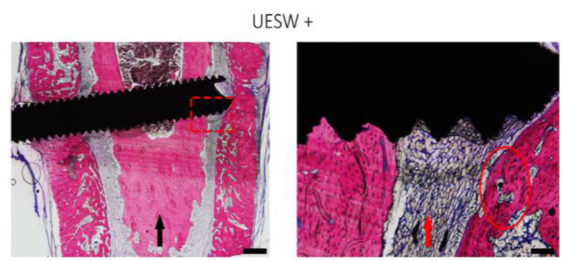
Biomechanical testing.



MicroCT analysis. Bone volume in specified areas (A and C) around the whole screw, (B and D) around the screw in the marrow) around cortical (a and b), and cancellous (C and D) screws.



Fluorochrome labeling. Bone mineralization (black arrow) only around treated screws and more periosteal mineralization (red arrow).

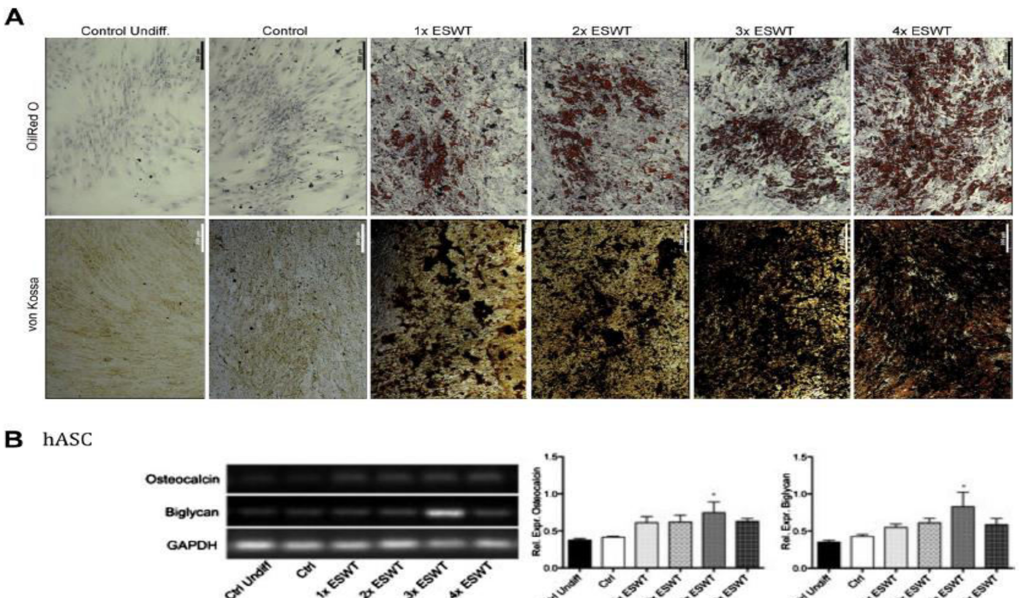


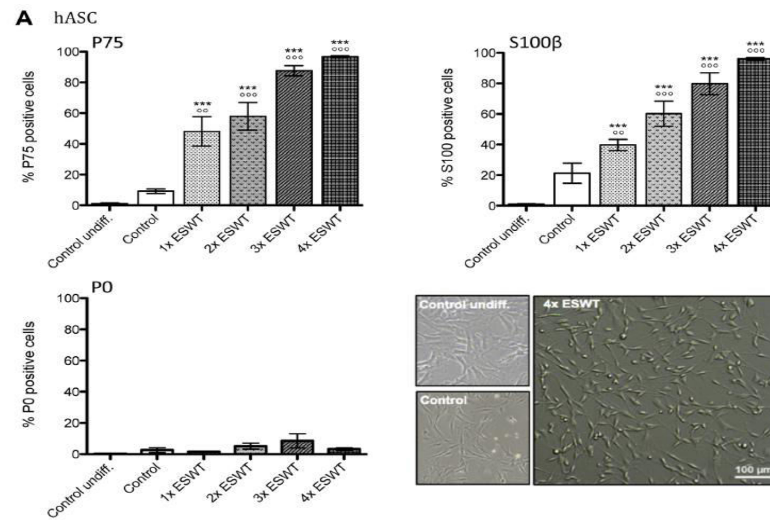
Histology. Neocortex after ESWT around a cortical screw. Original cortex (black arrow) and neocortex (red arrow).

SoftWave® Therapy – Stem Cell Stimulation

SoftWaves® improve stem cell quality

Schuh et al., 2014, „In vitro extracorporeal shock wave treatment enhances stemness and preserves multipotency of rat and human adipose-derived stem cells“





Repetitive SWT in vitro resulted in significant elevation of mesenchymal markers and increased differentiation capacity towards the osteogenic and adipogenic lineage as well as toward Schwann-cell like cells.

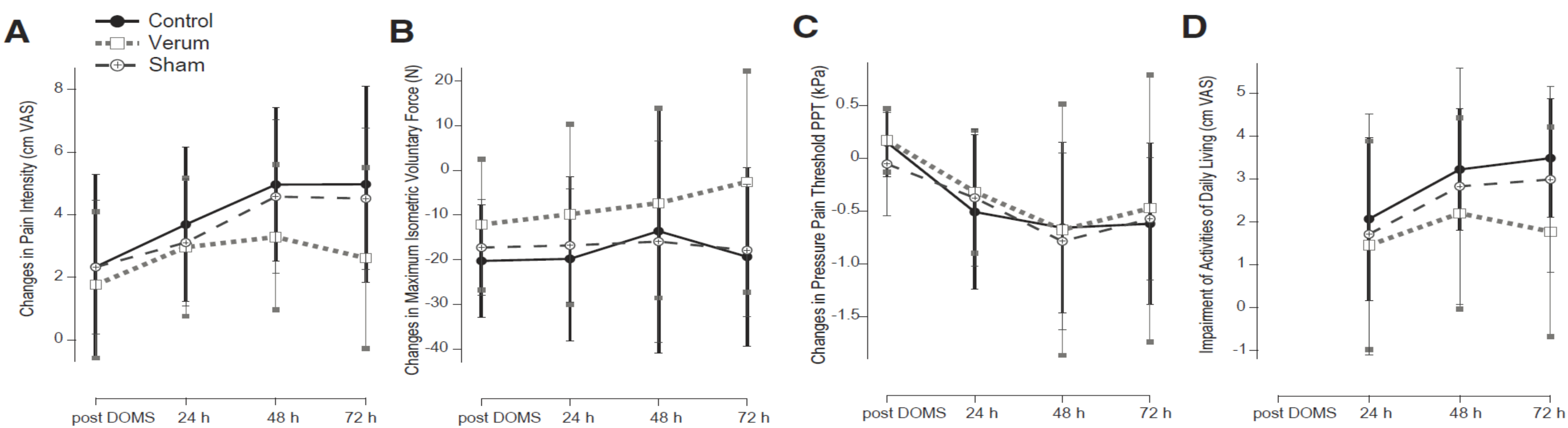
SoftWave® Therapy – Clinical Evidence

OrthoGold100®

J. Fleckenstein et al. (2017), Institute of Sports Sciences, Goethe-University Frankfurt, Germany.

"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"

46 patients randomly allocated to verum- (EFD 0.06 – 0.09 mJ/mm²; 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. The primary outcome was the difference in pain in tensity. Secondary outcomes included maximum isometric voluntary force (MIVF), pressure pain threshold (PPT), and impairment in daily life.



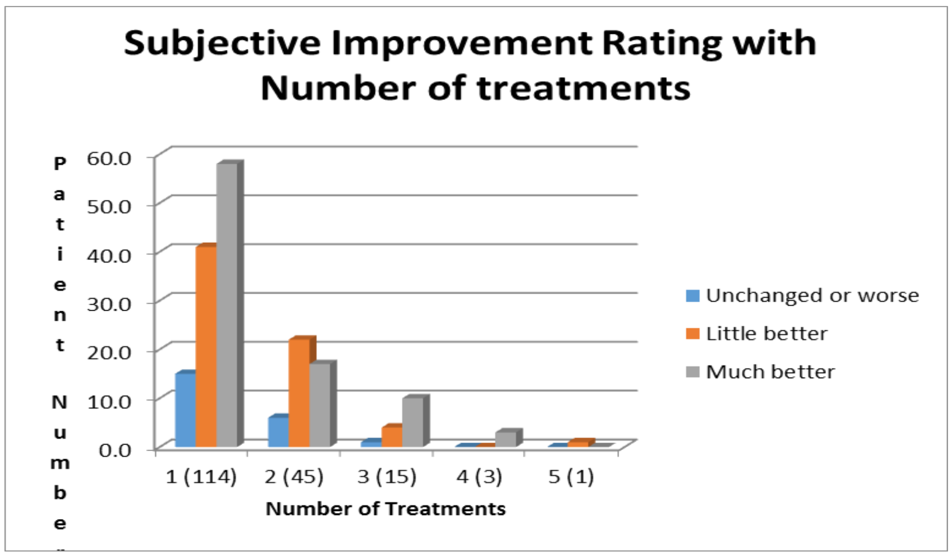
SoftWave® Therapy – Clinical Evidence

OrthoGold100®

Dr. A. Ngai (2016), Qatar Orthopaedic and Sports Medicine Hospital.

"Prospective cohort study examining short term changes in pain after application of Extracorporeal Shockwave Therapy (ESWT) in 178 consecutive patients"

- 178 patients (136 non-athletes, 42 athletes), 83 male; 95 female; 302 treatments.
- Chronic musculoskeletal injuries, pain score (VAS ≥ 3) and failure of conservative treatment.
- Incremental protocol dependent on tissue or injury (0.07-0.27 mJ/mm^2), 1000-1400 pulses given at 3-5 Hz.



Qatar Orthopaedic and Sports Medicine Hospital

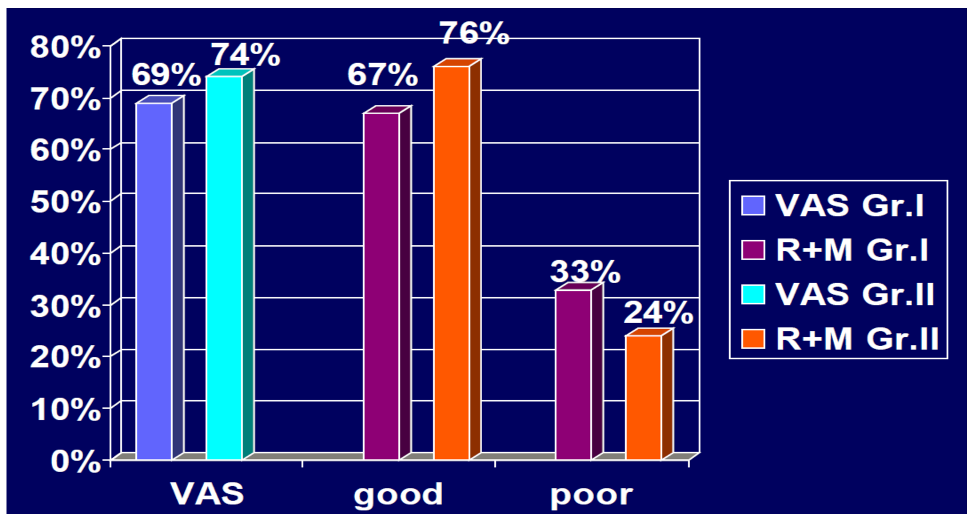
SoftWave® Therapy – Clinical Evidence

OrthoGold100®

R.Thiele, s. Marx (2009), IZS Berlin, Germany.

"Focused and planar focused ESWT – a comparison of the Results in the Treatment of Heel spurs"

Group I: Focused, 179 patients, 1200 shocks, 0.12 – 0.14 mJ/mm², 5 Hz, local anaesthesia.
Group II: Defocused, 95 patients, 1200 shocks, 0.14 mJ/mm2, 5 Hz, no anaesthesia.
Evaluation via VAS and Roles & Maudsley.



TRT Tissue Regeneration Technologies

SoftWave® Therapy – Clinical Evidence

OrthoGold280®

Dr. Wang (2004), Department of Orthopedics, China Medical University Hospital Taichung, TAIWAN.

"Clinical Application of Extracorporeal Shock Wave Therapy (ESWT) in The Treatment of Calcific Tendinitis of Shoulder, Plantar Fasciitis, Epicondylitis and Pseudarthrosis." *Randomized, controlled trial.*

Calcific tendinitis of the shoulder

- 31 patients,1000 shocks, 2 pulses/second with EFD 0.55 mJ/mm². 2 sessions, 2 weeks apart.
- Pain scale score decreased from 7.3±2.1 pre-ESWT to 3.5±2.2, 3.2±2.3 and 2.1±1.9 at 6 weeks, 12 weeks and 6 months post-ESWT in the ESWT group.
- Function scale score increased from 4.0±2.5 pre-ESWT to 7.2±2.6, 8.2±2.0 and 8.4±1.9 at 6 weeks, 12 weeks and 6 months post-ESWT in the ESWT group.
- Satisfaction was 74, 81, 80 % at 6, 12 weeks and 6 months post-ESWT.
- 43.5 % of the ESWT group and 0% of the control group showed partial or complete disappear of the calcium deposits radiographically.

Plantar fasciitis

- 37 patients,1000 shocks, 2 pulses/second with EFD 0.55 mJ/mm². 2 sessions, 2 weeks apart.
- Pain scale decreased from 7.2±1.7 pre-ESWT to 3.6±2.4, 2.0±1.1, and 1.2±1.2 at 6 weeks, 12 weeks and 6 months post-ESWT in the ESWT group.
- In the ESWT group, functional score increased from 39.8±15.2 pre-ESWT to 70.0±15.4, 85.7±12.6, and 96.1±6.3 at 6 weeks, 12 weeks and 6 months post-ESWT.
- Satisfaction rates are 76.9% (6-week), 84.6% (12-week), and 100% (6-month) post-ESWT.

Epicondylitis of the elbow

- 36 patients,1000 shocks, 4 pulses/second with EFD 0.2 mJ/mm². 2 sessions, 2 weeks apart.
- Pain scale score decreased from 6.3±2.1 pre-ESWT to 3.5±2.2, 1.7±1.5 at 6 weeks and 12 weeks post-ESWT in the ESWT group.
- Mayo elbow performance index (MEPI) increased from 69.7±12.2 pre-ESWT to 83.7±11.7, 89.2±15.5 at 6 weeks and 12 weeks post-ESWT in the ESWT group.
- Satisfaction was 86.6% in the ESWT group.

Pseudarthrosis

- 31 patients. Femur non-union 500 shocks at 1.30 mJ/mm². Tibia non-union 4000 shocks at 1.30 mJ/mm². Humerus non-union 3500 shocks at 1.30mJ/mm².
  Radius and ulna non-unions 300 shocks at 1.09mJ/mm². Metacarpal and metatarsal non-union 2000 shocks at 0.89mJ/mm².
- Pain scale score from 2.9±2.3 pre-ESWT to 1.5 ±1.6, 1.1 ±1.2, and 1±1.2 at 6 weeks,12 weeks and 6 months post-ESWT.
- Function scale from 5.5 ±2.2 pre-ESWT to 7 ±2.4, 8.6 ±2.9, and 6±3.4at 6 weeks,12 weeks and 6 months post-ESWT.
- Satisfaction percentage was 81, 83, and 80% at 6, 12 weeks and 6 months post-ESWT.

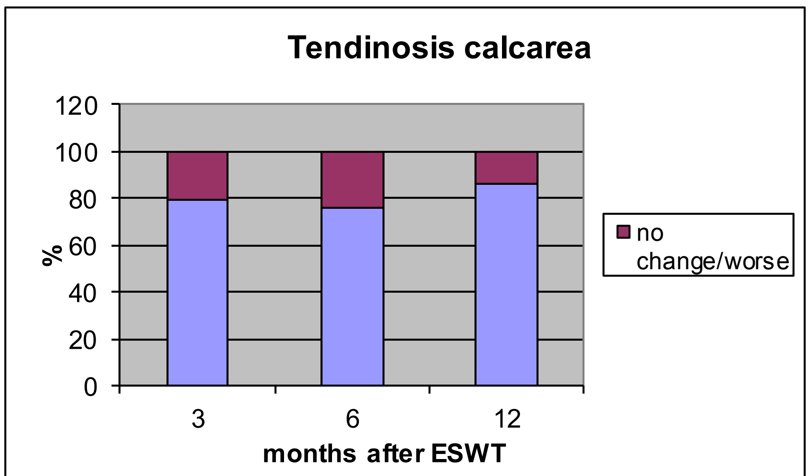
SoftWave® Therapy – Clinical Evidence

OrthoGold280®

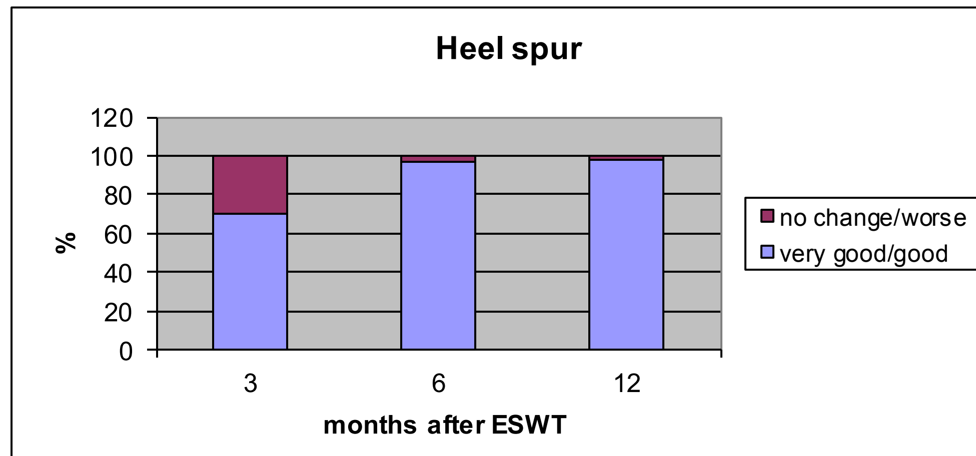
Dr. R. Diesch (2000), Bodensee Sports Clinic Friedrichshafen, Germany.

"Clinical Application of Shock Waves in the Treatment of Tendinosis Calcarea of the Shoulder, Plantar Fasciitis, Epicondylitis and Pseudarthrosis." I

170 patients were treated in a prospective study in accordance with DIGEST with the orthowave®.
Improvement measurement via the VAS and Roles & Maudsley score.



45 patients, Ø 2.3 treatments, 750 – 850 shocks, 0.75 mJ/mm²



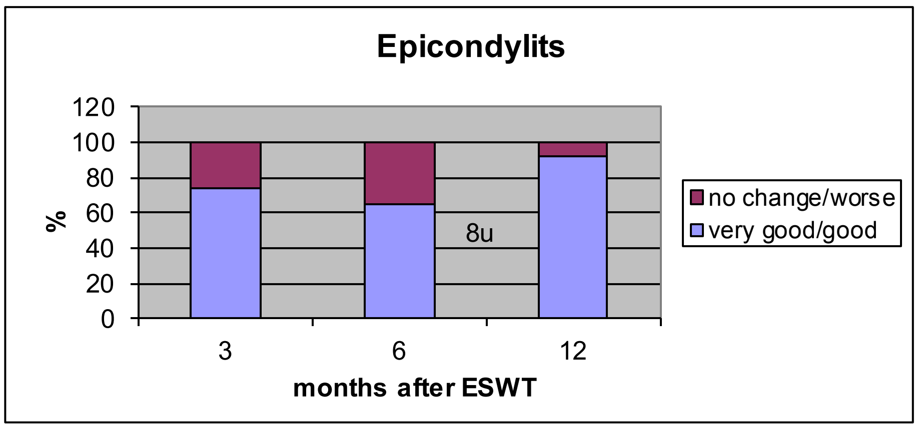
79 patients, Ø 2.2 treatments, 800 – 1000 shocks, 0.55 mJ/mm²

SoftWave® Therapy – Clinical Evidence

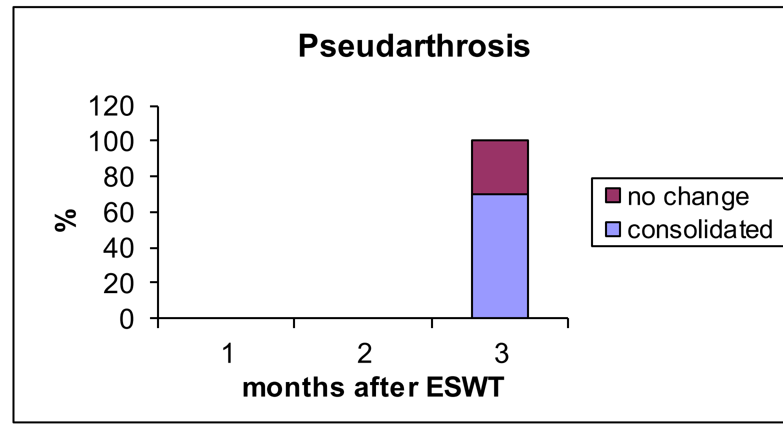
OrthoGold280®

Dr. R. Diesch (2000), Bodensee Sports Clinic Friedrichshafen, Germany.

"Clinical Application of Shock Waves in the Treatment of Tendinosis Calcarea of the Shoulder, Plantar Fasciitis, Epicondylitis and Pseudarthrosis." II



32 patients, Ø 2.4 treatments, 700 – 800 shocks, 0.2 mJ/mm²



14 patients, 1 treatment, 2000-3000 shocks, 1.09 mJ/mm²

The results show, that orthowave® delivers such very wide range of energy, that all standard indications can be treated. In this study, the total amount of energy applied in one session was in the range between 1,275 and 45,000 mJ and the results are as good or even better as compared with results published in literature.

SoftWave® Therapy – Therapeutic Effects

- Pain relief - analgesic effect
- Anti-inflammatory action:
  - Lowers the pro-inflammatory immune response
  - Reduces leucocyte and macrophage infiltration
- Decreases cellular apoptosis and reduces necrosis
- Anti-bacterial effect in the treatment of infections
- Induces the expression of endogenous growth factors
- Angiogenesis; improved vascularity and blood circulation, tissue supply ↑
- Lymphangiogenesis; improved physiological homeostasis
- **Ossification; formation of new bone tissue**
- Stimulates natural anabolic and growth functions in all kind of tissues (skin, bones, cartilage, smooth & striated muscles, nerves…)
- <u>Activation of stem cells</u>; metabolism ↑, proliferation ↑, migration ↑, differentiation ↑
- **Tissue remodelling and regeneration!**

SoftWave® Therapy – Conclusions

- SoftWave Therapy stimulates a number of fundamental and basic cellular regeneration processes

→ Tissue remodelling & healing!

- SoftWave Therapy helps to resolve the actual cause of the disease!
- Non-invasive and tissue-conserving SoftWave Technology!

→ No side- effects!

- Very powerful tool in **regenerative medicine!**
- SoftWave Therapy represents nearly unlimited treatment possibilities and applications in tissue activation & regeneration!

MTS Spark Wave® References I

A. Ngai (2016), Qatar Orthopaedic and Sports Medicine Hospital.
"Prospective cohort study examining short term changes in pain after application of Extracorporeal Shockwave Therapy (ESWT) in 178 consecutive patients"

KC Vincent, C d\`Agostino (2016), European College of Sports Science.
"Influence of medical shock waves on healthy muscle tissue."

M. Gleitz (2014), Orthopaedic Practice, Luxembourg.
"The Significance of Inflammatory Tendon Hypervascularization for the Treatment Results with ESWT: Are Actual recommendations Still Valid?"

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"Clinical Application of Extracorporeal Shock Wave Therapy (ESWT) in The Treatment of Calcific Tendinitis of Shoulder, Plantar Fasciitis, Epicondylitis and Pseudarthrosis." *Randomized, controlled trial.*

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"Clinical trial with orthowave280."

R. Thiele, S. Marx (2002-2005), IZS Berlin.
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TRT SoftWave® References II

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Publication title	Author
4th ISMST Basic research meeting 2016 in Vienna, Austria	
Low-energy shock waves treatment induces angiogenesis in ischemic muscle by stimulation of Toll-like receptor 3 signalling	Holfeld J. et al.
The effect of shock waves on in vitro cartilage development in silk scaffolds	Szwarc D. et al.
Shock wave therapy causes increased macrophage recruitment and enhances M2 polarization	Nägele F. et al.
20th International congress of the ISMST 2017 in San Sebastian, Spain	
P29. Shock wave treatment of muscle stem cells – a new implementation for regeneration	Fuchs C. et al.
P30. Shock wave treatment reduces neuronal degeneration upon spinal cord ischemia and improves symptomes in a first-in-man trial	Holfeld J. et al.
P31. Shock waves enhance neuronal survival and improve motor function after traumatic spinal cord injury	Tepeköylü C. et al.
P33. Shock wave therapy for osteoinduction	Koolen M. et al.

ESWT + PRP Synergy References

Notarnicola, A. ***et al.*** **Effect of shock wave treatment on platelet-rich plasma added to osteoblast cultures.** *Ultrasound Med. Biol.* **37**, 160–168 (2011).

→ Osteoblast cultures with PRP pretreated with SW showed increased expression of insulin-like growth factor binding protein 3 (IGFBP-3), runt-related transcription factor 2 (RUNX2), of collagen type I, osteocalcin and insulin-like growth factor 1 (IGF-1).

→ This suggests that ESWT should stimulate osteogenesis also by indirect platelets-mediated network. It therefore seems possible that combining the two methods, ESWT and bioengineering procedures to infiltrate PRP and growth factors, could be a successful app roach.

Seabaugh, K. A., Thoresen, M. & Giguère, S. Extracorporeal Shockwave Therapy Increases Growth Factor Release from Equine Platelet-Rich Plasma In Vitro. *Front. Vet. Sci.* (2017). doi:10.3389/fvets.2017.00205

→ ESWT significantly increased transforming growth factor-ß1 (TGF-ß1) and plateled derived growth factor ßß (PDGF-ßß) concentrations.

→ The combination of PRP and ESWT might result in synergism of two modalities previously utilized individually for tendon and l igament injuries.

THANK YOU!

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