# The biological effects of extracorporeal shock wave therapy (eswt) on tendon tissue

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## Summary

**There is currently great interest in the use of Extracorporeal Shock Wave Therapy (ESWT) and in clarifying the mechanisms of action in tendon pathologies. The success rate ranges from 60% to 80% in epicondylitis, plantar fasciitis, cuff tendinitis, trocanteritis, Achilles tendinitis or jumper's knee. In contrast to urological treatments (lithotripsy), where shockwaves are used to disintegrate renal stones, in musculoskeletal treatments (orthotripsy), shockwaves are not being used to disintegrate tissues, but rather to microscopically cause interstitial and extracellular biological responses and tissue regeneration. The researchers are interesting to investigate the biological effects which support the clinical successes. Some authors speculated that shockwaves relieve pain in insertional tendinopathy by hyper-stimulation analgesia. Many recent studies demonstrated the modulations of shockwave treatment including neovascularization, differentiation of mesenchymal stem cells and local release of angiogenetic factors. The experimental findings confirm that ESWT decrease the expression of high levels of inflammatory mediators (matrix metalloproteinases and interleukins). Therefore, ESWT produces a regenerative and tissue-repairing effect in musculoskeletal tissues, not merely a mechanical disintegrative effect as generally before assumed. Based on the encouraging results of clinical and experimental studies, the potential of ESWT appears to be emerging. The promising outcome after this non-invasive treatment option in tendinitis care justifies the indication of shockwave therapy. Further studies have to be performed in order or determine optimum treatment parameters and will bring about an improvement in accordance with evidence-based medicine. Finally, meta-analysis studies are necessary to demonstrate the efficacy and safety of ESWT in treating tendinopathies.**

*Key words: shock waves, tendon, tendinopathies, biological effects.*

## Introduction

A tendon is a tough band of fibrous connective tissue, that usually connects muscle to bone and is capable of withstanding tension (1). Microscopically, the main components of tendons are the cells (tenocytes) and the Extra Cellular Matrix (ECM) (collagen, elastin, and ground substance).
Due to overuse and trauma, tendons are subjected to tendinopathies. The "injury" generally results in inflammation and degeneration, or weakening, of the tendon, which may eventually lead to tendon rupture. It was believed, in the past, that tendons could not undergo to matrix turnover and that tenocytes were not capable of repair. However, it has been shown more recently that Matrix Metallo Proteinases (MMPs) have a very important role in the degradation and remodeling of the ECM during the healing process after a tendon injury. In response to repeated mechanical loading or injury, cytokines may be released by tenocytes and can induce the release of MMPs, causing degradation of the ECM and leading to recurring injury and chronic tendinopathies. A variety of other molecules are involved, on the contrary, in tendon repair and regeneration. There are five growth factors that have been shown to be significantly up-regulated and active during tendon healing: Insulin-like Growth Factor 1 (IGF-I), Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (b-FGF), and Transforming Growth Factor beta (TGF-beta).

### History and overview of shock waves therapy

Shockwaves are defined as pressure waves (or transient pressure oscillations), that propagate in three dimensions and typically induce a clear increase in pressure within few nanoseconds (4). There are very rapidly rising positive pressure impulses from 5 to 120 MPa in about 5 ns, followed by a decrease to negative pressure values of –20 MPa (5).
*Extracorporeal Shock Wave Therapy (ESWT)* was firstly applied in a patient in 1980 to disintegrate kidney stones (2). The possibility to disintegrate stones in urolithiasis by SW offered the transfer to pathological neo-calcifications in musculoskeletal disorders. Loew and Jurgowski first described calcific tendonitis of the rotator cuff in 1993 (3). The dissolution of calcium deposits documented by X-rays appears to increase therapeutic indications. At an early stage,

enthesiopathic neocalcifications of tendon insertion area of plantar fascia were reasonable enough to prompt exploration of the effects of ESWT in chronic plantar heel pain (4). The initial mechanical idea was to disintegrate the heel spur by ESWT, but no study exists reporting spur disappearance (5). However, clinical studies seem to indicate a high effectiveness of SW for treating painful plantar heel spur, with an average success rate of 81% (6). This success rate is superior to other conservative or operative treatment options (7). It is therefore not surprising that FDA approval has been granted for this indication for ESWT devices. Similar to fasciitis, lateral epicondylitis became part of experimental treatment with ESWT (8). Compared to plantar fasciitis, epicondylopathy showed a lower success rate of about 60% (9). Following, ESWT was applied to the other tendinopathies with a success rate ranges from 60% to 80% (10). Due to the disruption of the tissues, possibly observed with high-energy SW, the applied energies were increasingly lowered (10).

Physicians use the parameter of Energy Flux Density (EFD), to illustrate the fact that SW energy flows through an area with perpendicular orientation to the direction of propagation and its unit is mJ/mm2. Rompe et al. (11) classified the SW treatment on the basis of the EFD, as low (<0.08 mJ/mm2), medium (<0.28 mJ/mm2) and high (<0.60 mJ/mm2). Usually, the EFD applied in clinical practice ranges from 0.001–0.4 mJ/mm2 (12); at lower and medium EFD, Nitric Oxide (NO) is released and its antalgic, angiogenetic and anti-inflammatory effects are very useful in clinical treatment (12). Moreover, a relatively higher EFD is applied to treat pseudoarthrosis, localized in the femoral or tibial diaphysis or metaphysis, yielding a 72% success rate (13).

There is currently great interest in the use ESWT, and in ascertaining the mechanism of action of this kind of treatment, keeping in mind the good results reported in clinical practice (14). Some authors speculate that shockwaves relieve pain in insertional tendinopathy by hyper-stimulation analgesia (15). An initial increase and subsequent long decrease in substance P release from the treated region could, however, explain the initial pain during and shortly after shockwave treatment of tendon insertion and subsequent lasting relief from pain (16). However, it must be noted that substance P may also cause so-called neurogenic inflammations (17). Another hypothesis is therefore that following extracorporeal shockwave treatment there is evidence of decrease of this inflammation mediator concentration in the paratenon (18). More recently, the researchers are interested to investigate the mechanism by which physical ESWT promotion of tendon repair is linked to an increases in tenocyte proliferation and induction of growth factors.

ESWT has shown good results in the treatment of calcific deposits (14). While high-energy SW are expected to exert, in some way, a direct mechanical disintegration effect on calcareous deposits in the rotator cuff tendon (19), low-energy ESWT is regarded as a form of hyperstimulation analgesia. The mechanism of the therapeutic effect of ESWT on shoulder calcification is not certain. The hypothesis has been proposed that the increasing pressure within the therapeutic focus causes fragmentation and cavitation inside the amorphic calcifications, leading to disorganization and disintegration of the deposit (20). The disappearance of the deposit may be due to breakthrough into the adjacent subacromial bursa or local resorptive reactions in the surrounding soft tissue (21). In the treatment for chronic calcifying tendinitis of the shoulder, no significant differences were found between ESWT and arthroscopy: due to this consideration, shock wave therapy is preferred because of its non-invasiveness (14). Extracorporeal shockwave therapy has been also proposed in the treatment of Achilles tendinopathy, with encouraging short-term results. Some of the Authors obtained satisfactory results in 47.2% of cases at two-months follow-up, which increased to 73.2% at medium-term Follow-Up (FU), and then reaching 76% at long FU (22). ESWT is also a safe and promising treatment for patellar tendinopathy, with a positive effect on pain and function. Satisfactory results were reported in 73.5% of cases. In performing athletes, treatment was satisfactory in 87.5% of cases, with an average time of resuming sport of approximately 6 weeks (23). The studies have revealed comparable results of ESWT in patients with chronic tennis elbow compared with percutaneous tenotomy of the common extensor origin, showing success rates of 48%-72%. The overall results at one year are 62% excellent to good and 38% fair to poor. A substantial improvement of symptoms has been described to be achieved between three to 12 weeks after treatment, and this improvement is maintained at the one year follow-up (24).

**How does shock waves therapy work on tendon?**

The mechanism of action of SW is not yet completely understood. Many mechanisms have been described in explaining SW effects, including direct stimulation of healing, neovascularisation, direct suppressive effects on nociceptors and an hyperstimulation mechanism, that would block the gate-control mechanism. In spite of the initial studies, which showed high-energy SW treatment can induce fibrinoid necrosis, paratenon fibrosis and inflammatory cell infiltration in normal tendons (25), as well as an impaired tensile strength of tendons (26), more recent studies have demonstrated that SW treatment can increase the number of neovessels at the normal tendon–bone junction (27), through the release of growth factors and some other active substances (28). Even though ESWT has an history of more than 10 years of clinical applications in tendinopathy, relatively few experimental studies were done to understand its biological effects on tendon tissue. The researchers are working nowadays to describe the cellular and biochemical mechanisms by which SW can enhance tendon repair.

The first evidence that ESWT promotion of tendinitis repair coincides with an increases in TGFb1 and IGF-I. These growth factors have been found to up-regulate extracellular matrix biosynthesis by tenocytes (29). It has been proposed that these increased mitogenic and anabolic responses of tendon tissue can be responsible of the clinical success of SW treatment in resolving tendon pathologies (30). Tenocytes can respond to mechanical stimulation by increasing TGF-b1 gene expression (31). These findings seems to indicate that tendon tissue can convert SW stimulation into

biochemical signals via release of TGF-b1 and IGF-I for tendinitis repair (29-31).
In 2005 Caminoto et al. (32) evaluated the effects of ESWT on extra-cellular matrix components of affected ligaments in the hind limbs of horses, using ultrasonographic, ultrastructural, and immunocytochemical techniques. Compared with the untreated controls, ESWT-treated tissue had more small, newly formed collagen fibrils and a greater expression of Transforming Growth Factor beta, 4 weeks after treatment. These results have indicated that ESWT appears to facilitate the healing process. Moreover, TGF-b1 has been reported to act as a potent inhibitor of macrophages-induced extracellular matrix degradation and inflammation during the healing of a wound (33).
Bosch et al. (34) studied the effect of ESWT on biochemical parameters and tenocyte metabolism of normal tendinous structures in ponies. They found that, at 3 hours after treatment, glycosaminoglycan (GAG) and protein syntheses were increased. Moreover, the level of degraded collagen was increased. Six weeks after treatment, there was a decrease of degraded collagen and GAG contents, as well of the synthesis of all the measured parameters. DNA content had not changed in either tendon samples or explants after culturing. The authors supposed that the stimulating short-term effect of ESWT might accelerate the initiation of the healing process in injured tendons.
Berta et al. determined the effects of ESWT on normal fibroblasts *in vitro* (35). The treated fibroblasts showed an increase in proliferation. mRNA expression was also high for TGFbeta-1, for collagen type I and for collagen type III. These data seem to confirm that the main factors involved in the repair process of connective tissues are activated by ESWT (36).
Mechanical and physical impact on tissues exposed to SW has been found to depend on flux density of energy (EFD): low energy level with low impulses showed positive stimulatory effects, whereas the high energy level with high impulses had significant inhibitory effects (11, 25). At lower EFD shock waves treatment, up-regulation of proliferating cell nuclear antigen (PCNA), collagen type I, collagen type III and TGF-beta1 gene expression were observed, followed by an increases in NO production, TGF-beta1 release and collagen synthesis. Shock waves can stimulate tenocyte proliferation and collagen synthesis. These data supported that tenocyte proliferation is mediated by early up-regulation of PCNA and TGF-beta1 gene expression, endogenous NO release and synthesis and TGF-beta1 protein and then collagen synthesis (37). Han et al. (38) verified that the higher concentration of cytokines and MMPs, generally observed in diseased tenocytes, were down-regulated after shock wave stimulation. In a following study Bosch et al. (39) verified the effects of ESWT on matrix structure and gene expression levels in tendinous structures in ponies. After high energy treatment an histological disorganization of the normal collagen structure was observed. The degraded collagen levels increased at 3 hours post treatment and reduced after 6 weeks. The gene expression analysis for both collagen and MMP was found up-regulated at 6 weeks after treatment. These data can be considered indicative for repair phenomenons in tendinopathies. It should be necessary to restrict exercise in recently treated patients (22), considering the observed disorganization of the collagen network verified after ESWT (39).

## Conclusions

The experimental results show that ESWT significantly stimulated the ingrowth of neovascularization associated with increased expressions of angiogenic growth indicators in tendon, bone and tendon-bone interface. Neovascularization may play a role in the improvement of blood supply and healing of tendon. There is a close relationship between the decrease of substance P release and the clinically known treatment pain, with consecutive pain reduction in the shockwave treatment of tendon insertion diseases. Nitric Oxide appears to play an essential role in the molecular mechanisms of ESWT. Moreover, change of concentration of flogosis mediators supports an anti-inflammatory effect of this therapy. Therefore, it seemed likely that physical shockwaves raise the mechanotrasduction and convert into biological signals that lead to a cascade of biological responses in tendon. Further studies have to be performed to determine optimum treatment parameters and to bring about an improvement, in accordance with evidence-based medicine. Another interesting question of research should be to determinate which dosage have a therapeutic effect and which dosage induce an overdose effect. In conclusion, further meta-analysis studies will probably further support the efficacy and safety of ESWT in treating all kinds and level degree of tendinopathies.

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