CHAPTER 4

The Applied Mechanical Vibration as Extracorporeal Shock Wave

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Abstract: After its originary introduction as urological lithotripsy (still clinically applied), shock wave progressively gained a growing therapeutic importance in some different medical fields. Initially restricted in many musculo-skeletal disorders, in more recent years, thanks to a better knowledge about its mechanisms of actions (mainly antiflogistic, angiogenic and analgesic), this particular form of mechanical vibration nowadays represents a real innovative and unexpected therapeutic tool at the service of rehabilitation and regenerative medicine. The effectiveness, safety and ductility of shock wave therapy make it a unique and versatile strategy with further promising therapeutic perspectives in the near future.

Keywords : Focused and unfocused waves, Lithotripsy, Mechanical stimulation, Radial wave, Regenerative processes, Shock wave generators, Shock waves.

INTRODUCTION

Shock waves are a particular form of mechanical stimulation, whose first medical application was limited to the treatment (breaking up) of kidney stones (as extracorporeal shock wave lithotripsy). In the following years, it expanded to the musculo-skeletal field, mainly for the treatment of some tendon and bone diseases, and more recently some other important and revolutionary clinical applications in the field of regenerative medicine have been studied and introduced in clinical practice [1 - 3]. Nowadays, Extracorporeal Shock Waves

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Therapy (ESWT) represent a valid tool for a wide range of disorders, both in orthopedics and rehabilitative medicine (tendon pathologies, bone diseases, vascular bone pathologies), but also in dermatology and vulnology (chronic wounds, ulcers, scars) [4 - 19], neurology complications such us spasticity [20, 21], or some sexual disturbances (*induratio penis plastica* and erectile dysfunctions) [22 - 28], and cardiology (in relation to ischemic heart diseases) [29 - 32].

Based on its noninvasiveness, safety (as absence of main side effects) tolerability, repeatability, and efficacy (if properly applied), extracorporeal shock waves constitutes a unique therapeutic tool in a broad range of medical conditions, representing a very useful medical solution especially when other conservative or surgical treatments are ineffective or failing [33 - 35].

GENERAL CHARACTERISTICS OF SHOCK WAVES

Shock wave (SW) is a particular form of mechanical stimulation, firstly described, as physical entity, at the beginning of the 19th century; only two centuries later, during World War II, based on fortuitous findings, some researchers began to study their possible therapeutic application in humans (other than their technical usage), aimed to exploit their potential for breaking structures. In fact, besides some early experimental attempts for destroying brain tumors in 1960, the main interest was reserved to the fragmentation of kidney stones (urolithiasis), and, at the beginning of the nineties, in Munich, extracorporeal shock wave lithotripsy was applied for the first time [36].

Soon after, in 1991, still based on some occasional observations, it was discovered that, from a simple mechanical stimulation (shock waves), it is possible to induce some relevant medical effects, unexpected before that time, and related to a biological action. Valchanov and Michailov in 1991 described the successful treatment of bone healing disturbances by SW application (that is osteogenesis induction), as the first non-urological application [37]. This should be considered as a milestone in the evolution of SW therapy, that is the changeover from the "mechanical model" of extracorporeal shock wave lithotripsy to its application as "mechanotherapy" on living tissues in all extra urological fields, where mechanical stimulations are applied for therapeutic purposes, based on biological reactions, as described below [38].

Since 1991 until now, SWs rapidly spread as orthotripsy for many musculoskeletal disorders (mainly bone healing diseases and tendon disturbances), although still considered as a relatively "pioneristic therapy" until few years ago, especially as this technique was inherited from urological applications, where it acts as a pure mechanical force. Still having in mind the

"mechanical" action of breaking renal stones, at the beginning of the musculoskeletal applications and for some years later, the main interest was addressed toward calcifications disruption. Finally, in the early years of the new millennium, due to the discovery of its regenerative potential, and the increasing number of scientific results published in literature, the efficacy of SW as a biological tool was made clear (not only a pure mechanical one). From a general point of view, it was necessary to wait for some years, since the emergence of their originary successful clinical applications, to know a great deal about the mechanisms of action of SW at the tissue and cellular level, in order to explain many clinical therapeutic results.

SWs are acoustic waves, characterized by a pick pressure rises from the ambient value to its maximum within very few nanoseconds. SWs can be distinguished from some other acoustic waves (as ultrasounds for examples), due to their shape, characterized by initial high peak-pressure amplitude, rapidly followed by a drop to a negative value within few microseconds [39 - 45].

In 1997, the physical characteristics of SWs, used in the therapeutic fields, were established by a Consensus Conference, relative to the parameters recognized by numerous SW Scientific Societies [40] (Fig. **1**):

- rapid rise in pressure (< 10 ns);
- high peak pressure (up to 100 MPa);
- short-time duration (< 1000 ns).

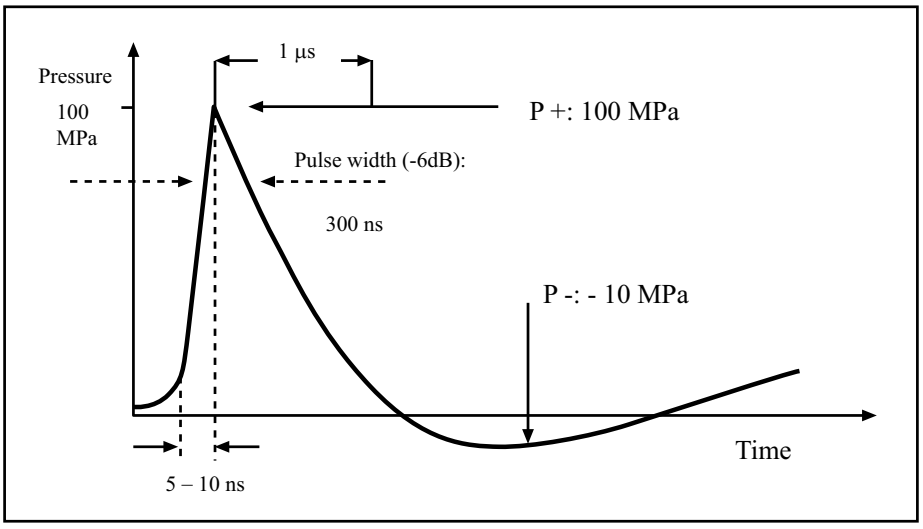

Fig. (1). ESWT: physical characteristics of wave. From: Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. Clin Orthop Relat Res 2001; (387): 8-17.

Both the negative and positive phase occur in a few seconds causing mechanical effects in transitional areas between tissues with different characteristics (acoustic impedance). The step of wave's deflection determines cavitation phenomenon with formation of bubbles gas that then subsequently implode at higher speed, thus generating a second front of shock waves or microjets of fluid (Fig. **2**).

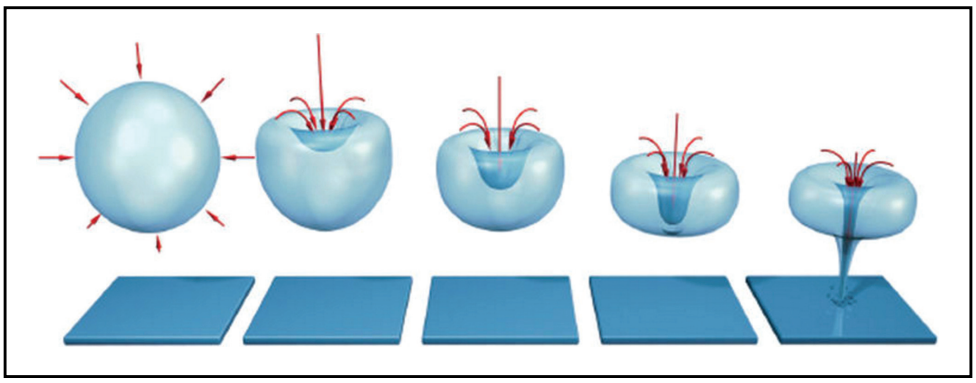

Fig. (2). Microjet formation by cavitation bubble collapse. From left to right: close to a boundary, the bubble cannot collapse symmetrically because the surrounding fluid cannot flow in symmetrically. Thus a torus is formed with a jet stream towards the boundary. From: Wess O, Ueberle F, Dührssen RN, *et al*. Working group technical developments – consensus report. In: Chaussy C, Eisenberger F, Jocham D, Wilbert D, Eds. High energy shock waves in medicine. Stuttgart, Thieme 1997; pp. 59-71.

These events are responsible, as the final result, for the direct (physical) and indirect (biological) effects of the shock waves on the treated tissues [39, 41, 43, 44].

Nowadays, in clinical practice, three different types of SW generators are available, equipped with different types of sources: electromagnetic, electrohydraulic and piezoelectric ones. In all these sources, SWs are produced due to a rapid increase in pressure (like a micro-explosion) into the water, and sooner, in order to obtain a therapeutic effect, they are concentrated or "focused" on the target (that is the pathological site of treatment). Focusing SW are realized by a parabolic lens, which directs the front of SWs, as soon as they originate from the source. Some technical characteristics of the different sources are described in more details below [42 - 44]:

- In the *electromagnetic generator,* the SW source is represented by a flat or a cylindrical coil (with multiple windings of copper wire) (depending on the model); at this level, a high energy transient electrical discharge induces a rapid expansion/contraction of the metal membrane of the flat coil or of the cylinder, thus generating SW.
- The source of the *electrohydraulic generator* is composed of two electrodes

(electrical terminals) located very close to each other in an aqueous environment, where a high energy transient electrical discharge passes (named "spark gap"). This causes a vapor bubble, that expands up to collapse sooner quickly, thus causing a wave of high pressure or SW (Fig. **3**).

- Differently, in the *piezoelectric generator*, the sources are composed of a set of piezoelectric crystals that instantly vibrate, as soon as a transient electrical discharge is produced. The rapid expansion and contraction of the piezoelectric crystals give rise to the SW front (Fig. **4**).

Fig. (3). Electrohydraulic generator of focused ESW, MTS Medical UG, Konstanz (Germany).

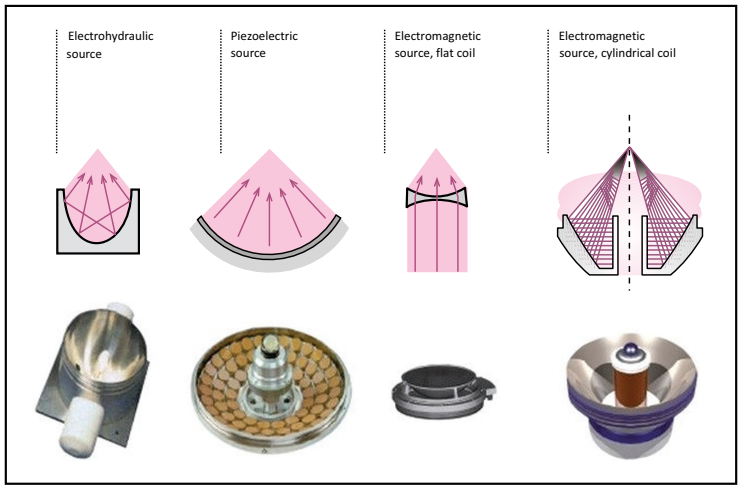

Fig. (4). Shock wave generators used in medicine. From: Wess O. Physics and technology of shock wave and pressure wave, International Society for Medical Shockwave Treatment Newsletter 2007.

From the technical point of view, some different types of lithotripters and sources will imply different treatment protocols, in relation to the number of impulses and the corresponding energy levels to be applied. On the basis of some standardized physical parameters, it is possible to describe the characteristics of different devices, trying, at least in part, to standardize and compare the different protocols with different focused SW source [42] (Fig. **5**).

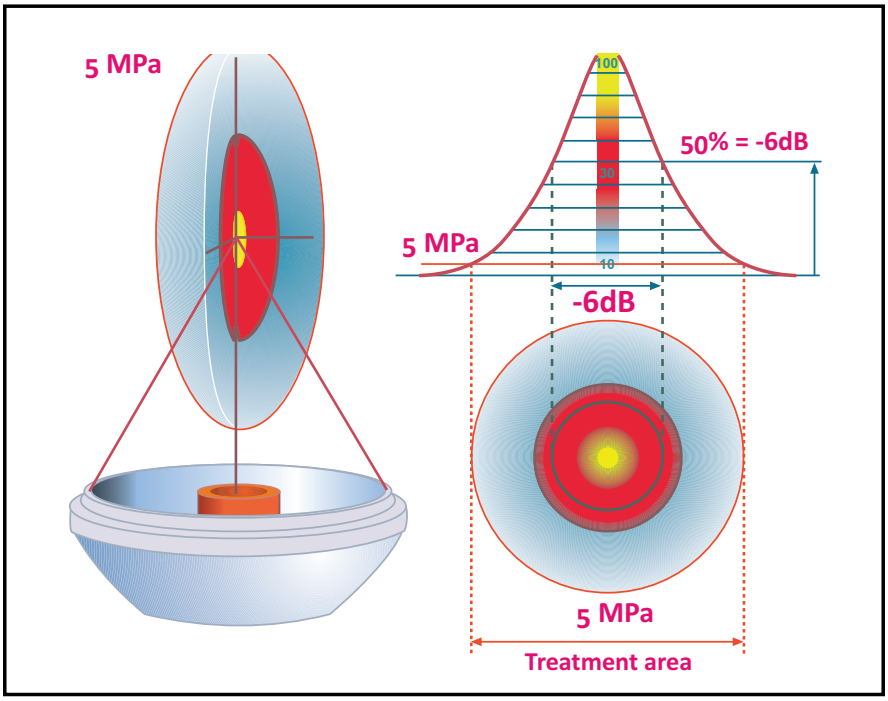

Fig. (5). Pressure distribution and focal zone. Typical focal zone (red) has an ellipsoid shape. Within the larger treatment zone (blue), therapeutic effects may still occur. From: Wess O. Physics and technology of shock wave and pressure wave, International Society for Medical Shockwave Treatment Newsletter 2007.

In more recent years, technological advances have supported the observations that SW could be effective also for tissue regeneration. To treat larger surfaces of tissue loss (as in ulcers, chronic or complicated wounds) some modified sources are needed, that although retaining the same physical characteristics (SW as such) are able to distribute the energy on a larger surface area. For this purpose, some focused SW generators were designed and marketed, being able to generate unfocused SW: the same biphasic wave assumes the form of a planar or unfocused wave during application. Obviously, for these devices the depth of penetration is lower, so that their therapeutic indication is limited to the more superficial lesions, like cutaneous ulcers and related disorders [2, 19]. Type of generator, energy flux density, frequency, number of pulses per square centimeter,

number of treatment sessions, and time interval between each session are further parameters to be modulated and compared [44, 46].

Besides focused SW and its planar version, based on scientific works and clinical practice, since many years, another form of mechanical wave, *i.e:* the radial wave, is successfully applied for many musculoskeletal diseases, especially of the soft tissues (Fig. **6**). Radial wave is an acoustic wave (that is a mechanical stimulation) as well, but generated in a different way. In this case, the source (or applicator) is constituted by a barrel hand piece, where, by means of compressed air or a magnetic field, a metallic bullet is accelerated at a very high speed. The high kinetic energy generated in this way makes impacts against the tip of the applicator itself, directly applied on the skin. Energy is accumulated during run and transferred directly to the body surface in the affected area. The so-produced wave, after impact, continues to propagate in the body as a ball-shaped wave which propagates in a spherical way, thus deriving the descriptive term of "radial wave". The energy produced by the pressure wave is highest at the level of skin surface, but spreads and weakens as it penetrates deeper. In the radial shock wave, the focal point is not centered on the target zone as in the focused SW, but on the tip of the applicator. Due to the mechanism of production, radial SWs are not focused in depth, but have a radial transmission mode limited to the more superficial layers of the body, which is applied for treatment. From the physical point of view, although both of them are acoustic or mechanical waves, they differ in term of the shape of the waves themselves. Moreover, they share some clinical indications, but differ from some other ones (see Chapter 2) [41 - 44, 47].

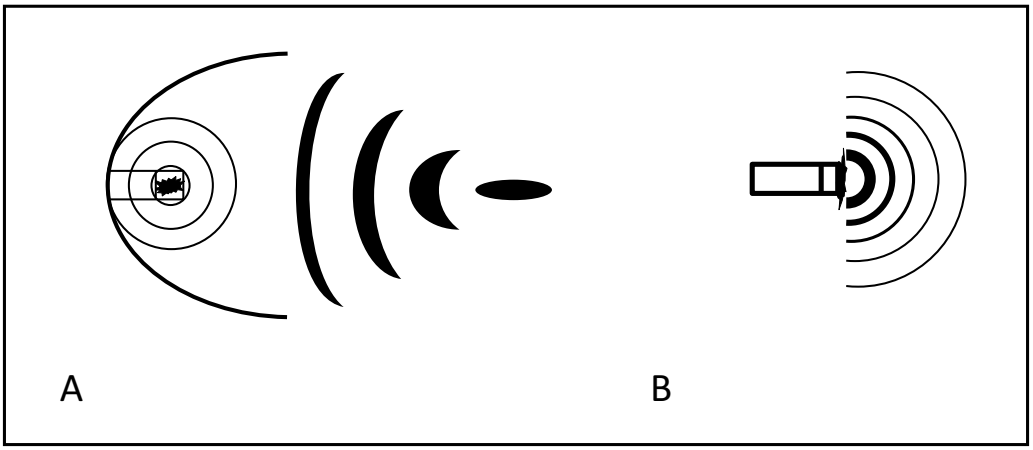

Fig. (6). A) Focused shockwave. **B**) Radial shockwave device. From: van der Worp H, van den Akker-Scheek I, van Schie H, Zwerver J. ESWT for tendinopathy: technology and clinical implications. Knee Surg Sports Traumatol Arthrosc 2013; 21(6): 1451-8.

Based on the tissue to be treated, (mainly soft tissues and bone), it can be appropriate to use a specific lithotripther rather than another one, relative to the different therapeutic requirements, especially the function of the energy to be applied while expecting a different biological effect. Low-medium energy level for treating tendon pathologies, or medium-high for bone [1, 2, 33] (Fig. **7**).

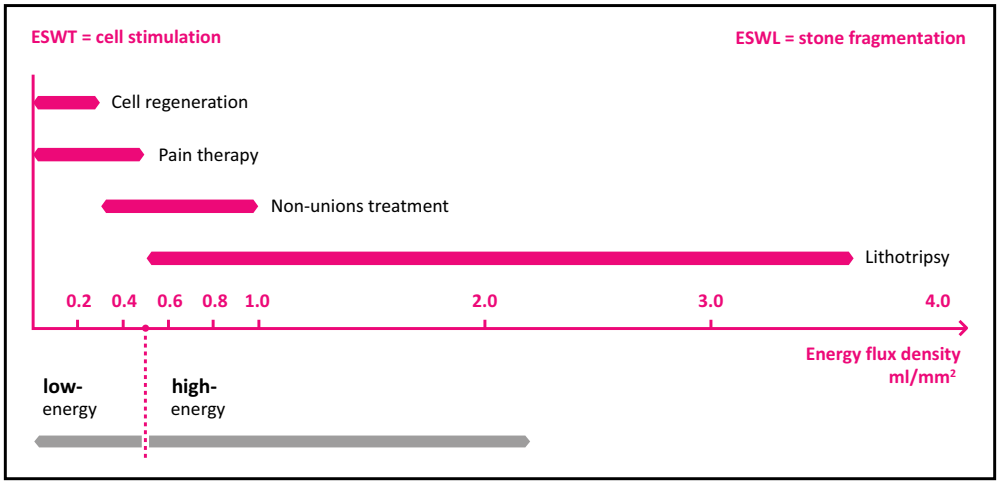

Fig. (7). Fields of application and relative energy levels of shock waves in medicine.

It is important to outline that, relative to the modalities of applying ESWT, international guidelines include all essential requirements for accurate application. If, for the treatments of bone disorders, it is important to target the anatomical area of pathology (better by fluoroscopic control), for those of tendons and related structures, this is not so primary. It could be, in any case, of great value to have a control "coupled" the system of generation of shock waves, in order to target SW precisely in the areas affected by degenerative processes, with/without calcifications, in this case the best instrumental method for targeting can be considered diagnostic ultrasound [48]. In spite of the type of device we use, if applied according to a good clinical practice, based on learning and training, from a general point of view, low-dose shock wave therapy without anaesthetic can be considered a safe and effective treatment [49 - 51]. Scientific literature or clinical experiences not report, systemic, or local complications [52].

MECHANISMS OF ACTION OF SHOCK WAVES

Nowadays, although partly unknown, there is a scientific evidence those SWs, on living tissues. Characterized with mechanical energy, do not produce some destructive or harmful effects, but properly make some biological actions on

living tissues and cells, thus exerting a positive and regulatory influence. Thus, the pure mechanical stimuli (mechanical energy) can be considered as the "trigger" or a *primum movens* of the biological reactions, rather than the direct responsible of the ultimate effects of the stimulation. Although still partly unknown, basic science articles and clinical experiences point out that the main mechanisms of action for the SWs in extra urological fields can be summarized as follows [1, 2, 33, 53]:

- small unmyelinated nerve fibers reduction;
- substance P dilution;
- nitric oxide (NO) production;
- changes in cellular membrane permeability;
- possible antibacterial effect (still under study);
- growth factors secretion and some other biological mediators;
- proliferation, migration and differentiation of stem cells.

Based on these mechanisms of action at the tissue and cellular level, these general important clinical results can follow [2, 53]:

- antiflogistic and anti-edema effects;
- angiogenesis and tissue-specific regeneration (especially skin and bone);
- analgesic effect.

As mentioned above, not all details of the biological mechanisms induced by SW application are completely known, partly they are still under study.

From a general point of view, mechanotransduction is possible as most of the cells of the body, due to surface receptors and other transmission signals, can perceive and transmit the stimuli to the nucleus, thus activating it with the final result of producing growth factors and some other biochemical substances. In the specific field of SW, these different biochemical substances are able to influence the processes of different cell lineages, besides inducing the formation of new small blood vessels. Specific stem cells of each tissue along with endothelial cells and their precursors can be activated. Angiogenesis (either from "scratch" or "budding" from pre-existing small blood vessels) is one of the basic condition for supporting regenerative processes in the different affected tissues [53].

In the past, the action of the extracorporeal shock waves was only relative to the mechanical effect, namely to the possibility of being able to destroy the ectopic formations in the tissues, today the therapeutic approaches are motivated by the knowledge of the biological and molecular effects that can be achieved by modulating the specific usage parameters [38].

Nowadays it is possible to apply in clinical practice some mechanical stimulations, better known as "vibratory mechanotherapies", both for many disorders of bone and soft tissues as well.

According to a revisited definition by Huang C *et al:* of the term and based on the current knowledge in mechanobiology, mechanotherapies include «all therapeutic interventions that reduce and reverse injury to damaged tissues, or promote the homeostasis of healthy tissues by mechanical means at the molecular, cellular, or tissue level». In other words, they include all «active mechano-interventions, that aim to convert potentially destructive mechanical effects into constructive influences and target normal mechano-adaptation to promote recovery» [38].

Therefore, it is evident that, within the framework of the mechanotherapy, Extracorporeal Shock Waves Therapy (ESWT) has a revealing importance in relation to a number of biological and molecular actions already discovered and to those which are still under study [38].

Its importance, as mechanotherapy, is related to the possibility of positively influencing some cells metabolism and functionalities, so it is possible to improve repair and regenerative process. A number of recent studies, in fact, underline as its effect is manifested as ability to stimulate stem cells proliferation, migration and differentiation, thus obtaining tissue healing and regeneration. Moreover, other than stem cells and bone marrow – stromal cells, some different lines can be a sensible target of mechanotrasduction pathways following SW stimulation, including tenocytes, bone cells, endothelial cells, fibroblasts, some other ones, including all their direct precursors [1 - 3, 54 - 63].

The neoangiogenetic capacity, could be related to an initial inhibition of endothelial cells apoptosis and adhesion, described *in vitro* in the very early phase (first 3 hours), after SW stimulation. It has been postulated that, some early gene responses of endothelial cells to SW, as mechanotherapy, are similar to those induced by the laminar shear stress flow that is characterized by an anti-apoptotic effect as well. To elaborate, although at 3 hours after SW application, there is no neoangiogenic activity (observed as it will appear after 12 hours), there are already some "warning" or "preparatory" signals, like downregulation of cell cycle and adhesion genes, perhaps related to an oncoming detachment of endothelial junctions [57].

Moreover, increasing scientific evidences seem to describe that SW mechanotransduction pathways are not only dose-related but can also differ various cell types and stem cells in different stages of differentiation. As a possible consequence, each cell lineage seems to be responsive to SW stimulation; but, probably, it exists a different and specific pattern and range of

optimal mechanical stimulation, being able to evoke some different biological responses, as much as the up regulation of TGF beta-1 (TGF-β1) and NO expression, other than suppression of the nuclear factor kB (NF-kB) activity and pro-inflammatory cytokines production [38, 54, 55, 64 - 66].

In very recent animal studies, aimed to evaluate the possible antifibrotic effect of SW application, used intramuscular injection of silicone, reduced formation of the dense fibrous envelope was described. Moreover, when applied in multiple SW treatments, it was possible to obtain active degradation of the fibrous capsule, due to synergistic modifications in pro- and anti-fibrotic proteins (TGF-β1 and matrix metalloproteinase 2, respectively), thus underlining a possible role of SW in reducing capsule formation and inducing fibrotic tissue resorption/remodeling as well [67, 68].

While describing the mechanisms of action of ESWT, based on similar experimental and clinical data, it hypothesize that this mechano-therapy would be able, not only to improve the healing events, but also to give rise to some regenerative processes; above all where fibrous tissue can be reduced at the source, or in any case, can be later remodeled (as in scar tissue).

These preliminary observations seem to foresee some further interesting applications in clinical practice, especially in cardiology, where some studies are already being conducted where regeneration of the original tissue, instead of scar tissue, is fundamental for heart vitality. On the other hand, many recent evidences would indicate that ESWT can ameliorate ventricular function in heart failure and ischemic diseases [69 - 71].

Moreover, recent studies in SW mechanobiology and basic science suggest that SW would influence the Toll-like receptor 3 (TLR3) pathway [69], suggesting its role in inducing tissue regeneration and remodeling as mechanotherapy, other than implying the role of this mechanotherapy as immunomodulator in wound healing, mainly through an anti-inflammatory pathway [30, 66, 72 - 74].

Surely, the most revolutionary evidence can be considered the data about the possible effect of SW on macrophages activities, in particular on the pro-resolving macrophages (or M2), that are able, at the crossroad between inflammation and regeneration, to induce resolution of the pathologic inflammatory processes at the tissue levels, thus increasing the possibility of a regenerative action [75].

Some studies showed how ESWT and the related mechanotransduction are effective in stimulating several endogenous growth factors such as epidermal growth factor, insulin-like growth factor 1, vascular endothelial growth factor

(VEGF) and NO production, inducing angiogenesis and promoting the healing of tendons, muscles, cartilage, bone and skin, fractures, ulcers and complex lesions.

Vulpiani *et al:*, [76, 77] described the clinical effectiveness of ESWT in Jumper's knee and in Achilles tendinopathy.

Saggini *et al:*, [78 - 80] showed the long-term effectiveness of ESWT in the rotator cuff syndrome and in jumper's knee.

Wang [81] highlighted the effect of increase in the performance of the knee after ACL reconstruction surgery, confirming the evidence of efficacy of this treatment in tendon and ligament diseases.

The efficacy of unfocused shock wave to improve "regenerative" processes was be demonstrated in a study by Saggini *et al:*, on retracting scars of the hand [82]. Selected patients were randomly divided into four groups (group A to D): group A (30 patients), consisting of individuals with (Group A-II, 15 patients) or without (Group A-I, 15 patients) surgery-induced complex regional pain syndrome (CRPS) of the hand; this group was administered treatment with unfocused ESWT alone, at a frequency of two sessions per week for 5 weeks; group B (15 patients with no evidence of CRPS) was treated with a combination of ESWT and manual myofascial therapy at a frequency of two sessions per week for 5 weeks; group C (15 patients with no evidence of CRPS) received ESWT treatment associated with manual myofascial therapy and local treatment with I-Coon system at a frequency of two sessions per week for 5 weeks; group D (10 patients with no evidence of CRPS) did not receive any treatment. Focal depth of shock waves was 49 mm with a total energy applied for each impulse of 0.13 mJ/mm^2; treatment frequency was 6 Hz and duration of each session was 1.5 min (500 pulses for session per 360 impulses/min), with a focus where the scar was hypertrophic and very painful. Scar assessment and evaluation were performed before the beginning of the treatment cycle (T0), after the fifth treatment session (T1) and after the second week, after the end of the 10th treatment session (T2). Scar height (cm), pigmentation, vascularization and pain were assessed using the modified Vancouver Scar Scale. Rating of subjective pain was performed using the Visual Analogue Scale (VAS); the VAS score is a simple tool commonly used for the evaluation of changes in pain intensity, with values ranging from 0 (no pain) to 10 (worst pain ever). Deficit in passive mobility because of scar-related contractures was evaluated using a range of motion (ROM) score ranging from a minimum of 0 to a maximum of 100. Biopsy specimens were taken from pathologic scars treated with unfocused ESWT at T0 and T2. A 3-mm, wedge-shaped incisional biopsy was collected from treated areas, perpendicular to clinically palpable scars, and sent for tissue processing and staining. Significant improvements were

observed in group A (treated with shock waves): the most important change was detected in skin biopsies. Histopathological examination (Fig. **8**) revealed significant increase in dermal fibroblasts in each active treatment group (*i.e:*, groups A, B and C), as well as in neoangiogenetic response and type I collagen concentration; likewise, in each active treatment group, significant qualitative improvement in dermal collagen was observed, with a finer and more fibrillar appearance. Staining with picrosirius red indicated that treatment with ESWT resulted in a collagen fiber arrangement parallel to the skin surface and replacement of type III collagen with type I collagen (thus restoring the physiologic relationship between type I and III collagen).

Immunohistochemical comparison of pre- and post-ESWT treatment biopsies revealed that administration of a shock wave regimen resulted in a significant increase in infiltrating fXIIIa-positive fibrocytes, CD34 dermal expression and CD31-positive small vessels.

By contrast, no significant changes were observed in the control group (group D) by either hematoxylin-eosin, picrosirius red or immune-histochemical staining.

The results of this study seem to confirm that shock wave treatment is capable of inducing an increase in the number of activated fibroblasts, CD34-positive fibrocytes and fXIIIa-positive dendritic cells. This process is thought to lead to the deposition of new collagen, characterized by thinner collagen fascicles and parallel orientation to the dermo-epidermal junction. Additionally, shock wave therapy may be regarded as playing a significant role in increasing CD31-positive vessel density in the dermis of treated patients, allowing an improved tissue metabolism.

In healthy human skin, type I and III collagen have relatively substantial roles during collagen formation, comprising 80-85% and 10-15%, respectively. Newly developed scars undergo a maturation process, with type III collagen being gradually replaced by type I collagen to restore normal type I-to-III collagen ratio (which is approximately 5:1). Into repair process of skin as well as tissue tendon collagen is a fundamental element for the tone and elasticity. A variation of the characteristics and amount of collagen can result in a pathological repair process and pathological scarring. Collagen fibers within scar dermis show a reduced resistance potential, being only 70% in the normal skin. Our studies on skin and pathological scars demonstrated and confirmed the biostimulating effectiveness of ESWT on skin through modulation of the 3 phases of tissue repair (inflammatory, proliferative, remodeling). The principle effect is restoring the normal relationship between type I and III collagen. Therefore, the fibroblasts are the most mechano-

responsive cell type and play a key role in the remodeling of the extracellular matrix synthesizing and reorganizing the connective tissue components.

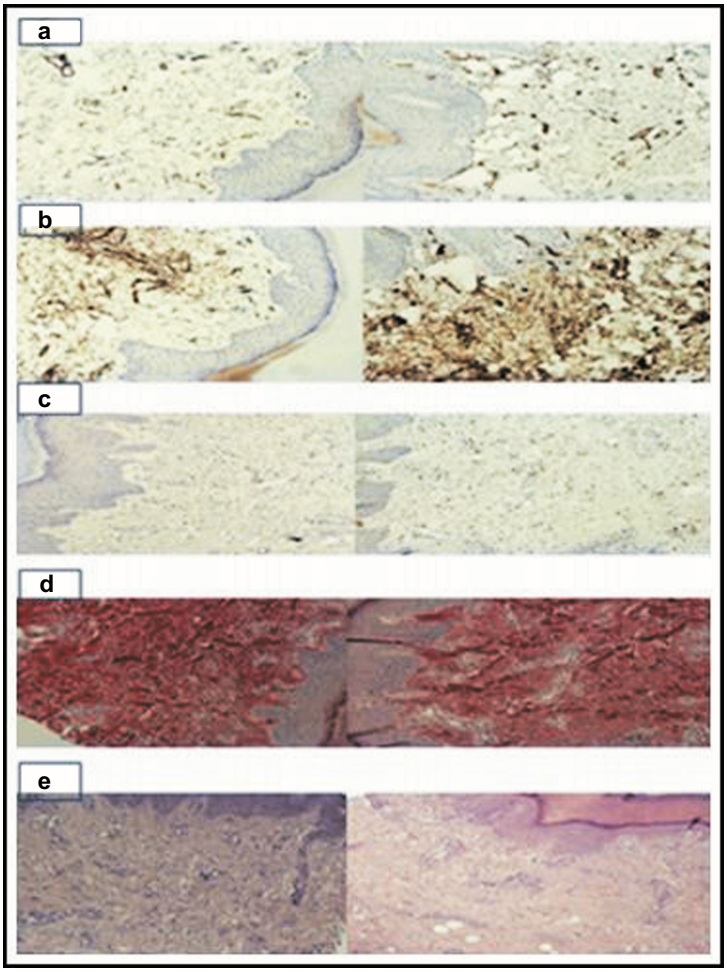

Fig. (8). Biopsy specimens taken from patients in the group treated with ESWT. (a) Immunohistochemical staining of fibroblasts and angiogenesis (right, before the treatment; left, after treatment) for FXIII reveals a significant increase in FXIII1 dendrocytes after treatment with ESWT. (b) Immunohistochemical staining for CD34 of fibroblasts, type I collagen and angiogenesis (right, before the treatment; left, after treatment) shows a significant increase in CD341dendrocytes and CD341vessels after treatment with ESWT. (c) Immunohistochemical staining for CD31 of angiogenesis (right, before the treatment; left, after treatment) demonstrates a significant increase in CD311 vessels after treatment with ESWT. (d) Picrosirius red (right, before the treatment; left, after treatment) staining reveals modified arrangement of collagen fibers after treatment with ESWT, parallel to the epidermis, and increased type I-to-III collagen ratio. (e) Hematoxylin-eosin (right, before the treatment; left, after treatment) highlights significant improvement in dermal collagen after treatment with ESWT, showing a thinner and more fibrillary collagen. From: Saggini R, Saggini A, Spagnoli AM, *et al:* Extracorporeal Shock Wave Therapy: An Emerging Treatment Modality for Retracting Scars of the Hands. Ultrasound Med Biol 2016; 42(1): 185-95.

Maffulli, in 2011 [83], described how changes in tendon structure in overload diseases (cit.) "are represented by: degeneration, disorganization and thickening of the collagen fibers, increase in degradation of collagen and interfibrillar glycosaminoglycans and, in particular, by altering of the normal relationship between type I and III collagen, as observed in the skin." Compatibly what has been observed in human skin, tissue regeneration is related to fibroblast infiltration and collagen remodeling, and based on the evidence of clinical efficacy of ESWT on the tendon, we can assume the existence of a similar reparative model *in vivo* in human tendon.

Mechanotransduction pathways and mechanobiology can also be advocated to describe and explain the analgesic effect of ESWT, more evident in the more precocious phases of application. Regarding this topic, recently Saggini *et al*:, described the effects of mechanotransduction on pain [84]; various hypotheses have been formulated, although one of the most reliable one is the theory of the "hyperstimulation analgesia". This theory states that a painful stimulation, as it can be in the case of SW, is soon transmitted to the central nervous system through the posterior column of the spinal cord, and it may activate the descending inhibitory system; it in turn blocks the transmission of nociceptive stimuli in the posterior column. Moreover, analgesia obtained can also improve the joint function as well. SW can also induce overstimulation of the nerve fibers, thus resulting in the increase of the painful stimulus and meanwhile intensifying the analgesic effect ("gate control" theory) [85].

Another biological explanation for the analgesic effect of SW application can be considered a possible degeneration of the nerve fibers originating from the small neurons immunoreactive to Activating Transcription Factor 3, a protein linked to the activation of genes related to protein coding pro-inflammatory, which seems to derive a relieved pain. Releasing of these bioactive substances (mainly substance P and calcitonin gene-related peptide) at the level of sensory nerve endings plays an important role in the maintenance of pain and chronic inflammation [86].

Chronic inflammation can contribute to increase the pain, for example in epicondylitis, chronic plantar fasciitis and tendinous disorders of the rotator cuff [87, 88]. A study revealed the contribution of substance P (as interleukin 1-alpha and TGF-β1) in the pathogenesis of tennis elbow, without any apparent infiltration of inflammatory cells [89].

From a general point of view, it likely that the mechanisms of action of SW in the treatment of musculoskeletal pain cannot be defined in a single pathogenetic mechanism, thus posing a demand for further studies. Nevertheless, all researches

conducted on muscle pain during the last years, and the experience gained in ESWT clinical practice for musculoskeletal pain, confirm the important role of this "mechanotherapy" as a conservative treatment option, which can also be applied to some other diseases characterized by functional disorders and pain syndromes.

CLINICAL GUIDELINES

The different therapeutic indications for SW treatment are described in the guidelines by the Società Italiana Terapia con Onde D'urto (SITOD) and the International Society for Medical Shockwave Treatment (ISMST).

Regarding the SITOD guidelines, all the following indications are considered.

- Standard indications
  - Pseudoarthrosis or delayed bone healing
  - Stress fractures
  - Shoulder tendinopathies (with or without calcification/s)
  - Chronic enthesopathies (insertional tendinopathies)
  - Plantar fascitis (with or without heel spur)
  - Early aseptic osteonecrosis
  - Early dissecans osteochondritis (after closure of the metaphyseal plates)
  - Algoneurodystrophy (Sudeck's disease)
- Relative indications
  - Miofascial syndromes
  - Muscle injury without discontinuity
  - Skin ulcers
  - Spasticity

In SITOD guidelines, it is reported that one of the most important factors to be considered for obtaining the best results is to formulate a correct diagnosis, as well as to exclude from ESWT, all those patients who present the following contraindications:

- Local bone or soft tissue acute infection;
- Primary pernicious diseases;
- Growth plates in the focal point (if high energies are applied);
- Disorders of coagulation;
- Pregnancy;
- Pacemaker;
- Presence in the focal point of brain, spinal cord, main nerves, lung tissue (neurocranium, spinal column, ribs).

On March 2008, a Consensus Conference by ISMST stated that «scientific results (both experimental and clinical ones) are related to the different parameters of the SW sources, single and total energy applied, to the modalities of targeting, to the frequency of the applications and the aim of the treatment (calcium deposits dissolution, connective tissue angiogenesis and pain therapy)» and that all the clinical and therapeutic general principles of orthopedic medicine and rehabilitation have to be taken into account while applying ESWT. According to this Consensus Conference, ISMST classifies all the general indications as follows.

- Approved standard indications by ISMST (indications are exactly reported as described by the guidelines)
  - Chronic tendinopathies
    - Plantar fasciitis with or without heel spur
    - Achilles tendinopathy
    - Radial epicondylopathy (tennis elbow)
    - Rotator cuff diseases with or without calcification
    - Patella tendinopathy
    - Greater trochanteric pain syndrome
  - Impaired bone healing function
    - Delayed bone healing
    - Stress fractures
    - Early stage of avascular bone necrosis (native X-ray without pathology)
    - Early stage osteochondritis dissecans post-skeletal maturity
  - Urology
    - lithotripsy (extracorporeal and endocorporeal)
- Common empirically-tested clinical uses
  - Tendinopathy
    - Ulnar epicondylopathy
    - Adductor syndrome
    - *Pes anserinus* syndrome
    - Peroneal tendon syndrome
  - Muscular pathologies
    - Myofascial syndrome (fibromyalgia excluded)
    - Injury without discontinuity
  - Impaired wound healing
  - Burn injuries
  - Salivary stones
- Exceptional indications/expert indications
  - Spasticity
  - Early stage osteochondritis dissecans pre-skeletal maturity
  - Apophysitis (Osgood Schlatter disease)

    - La Peyronie's disease
- Uses under experimental conditions
    - Myocardial ischemia (extracorporeal/endocorporeal)
    - Peripheral nerve lesions
    - Abacterial prostatitis
    - Periodontal disease
    - Osteoarthritis

According to the ISMST guidelines, while considering the results of ESWT, some important factors can have a positive influence:

- experience of the physician/SW therapist;
- possibility to use a proper device;
- correct therapeutic choice in the context of an integrated personalized program.

On the other hand, clinical results after ESW therapy can be negatively influenced:

- when exclusion criteria have not been respected or when there is not a general consensus about them;
- if there are some secondary orthopedic diseases;
- if there are some secondary not orthopedic diseases;
- according to the level of chronicity.

From a general point of view, ESWT can be classified in two main sections, accordingly to the type of tissue to be treated and consequently, to the different energy levels and number of impulses needed for the therapy. We distinguish the soft tissue treatments (such as those for tendons, muscles and skin) on one hand, while on the other hand, those for bone (mainly pseudoarthrosis/bone healing disturbances and bone vascular diseases, as osteonecrosis and bone marrow edema syndromes).

In the group of the soft tissues diseases for ESWT, tendinopathies play undoubtedly a predominant role in rotator cuff tendinopathies of the shoulder, lateral epicondylitis (or tennis elbow), medial epicondylitis (or golfer's elbow), plantar fasciitis (or heel spur), as well as Achilles tendinopathy and trochanteric syndromes [1, 3, 4, 8, 53].

It is useful to remember that the aim of this mechanotherapy on living tissues is not to make a pure mechanical (or "destructive") effect, but rather determine some positive biological pathways. Calcification can disappear in some cases (more evident for shoulder, for example), due to dissolution (that is a biological action), not for direct fragmentation or disruption of the calcium deposits. A similar

mechanism can be advocated for explaining the regenerative potential of SW in bone healing disturbances: osteoregeneration capacity is not due to micro-fractures induced by SW, but rather to a direct stimulation of bone cells, local stem cells and endothelial precursors, thus improving callus maturation and new bone formation as well [1, 3, 4, 8, 53].

The effectiveness of ESWT in the treatment of chronic tendinopathy is reported in many clinical trials have evaluated the efficacy in the treatment of rotator cuff syndrome, epicondylitis, plantar fasciitis, and other tendinopathies.

Although ESWT has been reported to be effective in some trials, in some other ones, it was not more effective than placebo.

The multiple variables associated with this therapy (besides the possible heterogeneity of the disease), such as the type of SW source, amount of energy delivered, method of focusing the shock waves, frequency and timing of delivery, and whether or not anesthetics are used, make it difficult to compare some different clinical trials [89].

Since from a biological point of view, (especially *in vitro* and animal experiments) nowadays there seem to be many valid and incontrovertible scientific evidences of a direct action of SW on tendon structures and cells, a statement of Rompe and Maffulli seems gaining more and more value. In 2007, Rompe and Maffulli [90] concluded that (cit.) «with current studies heterogeneous in terms of the duration of the disorder, type, frequency and total dose of SWT, period of time between SWT, type of management and control group, timing of follow-up and outcomes assessed, a pooled meta-analysis of SWT for lateral elbow tendinopathy was considered inappropriate. In a qualitative systematic per-study analysis identifying common and diverging details of 10 randomized-controlled trials, evidence was found for effectiveness of shock wave treatment for tennis elbow under well-defined, restrictive conditions only».

It could be stated that some different parameters could influence the results, in designing clinical studies, due to their high variability and heterogeneity, especially among different individuals.

Very recently again, Dingemanse *et al:* wrote that to draw more definite conclusions, high-quality randomized controlled trials, examining different intensities, are needed, as well as studies with long-term follow-up results [91, 92].

Finally, it is possible to reasume some variables, responsible for affecting clinical results:

- disease duration
- different devices and different ESWT protocols, not always perfectly comparable (according to frequency and total dose of SW energy);
- type of treatment and control group;
- timing of follow-up;
- clinical evaluation scales

It seems that the reason of controversial results in literature regarding the success of ESWT in tendinopathies could not be a biological matter but rather a methodological one [93]. When considering, for example, well-designed randomized control trials for tennis elbow, there has been demonstrated evidence of the effectiveness of shock wave intervention [94].

This seems to be more proper nowadays, as, since that time, some other basic science studies were published, describing a positive influence of SW on tendon cells and metabolism, that can be added to the well-known anti-inflammatory effect, proving physiological vascularization at the tendon-bone junction [33, 93].

All the beneficial effects deriving on tenocytes and tendon metabolism after SW exposure can be summarized as follows [94 - 99]:

- the release of nitric oxide (NO) activates protein synthesis and increases the expression of TGF-β1 gene and the increased production of cell nuclear antigen (PCNA): these processes result in an increase in the number of tenocytes and collagen synthesis;
- decreased expression of several interleukins (ILs) and metalloproteinases (MMPs);
- possible influence on tendon healing and regeneration;
- increased expression of lubrycin;
- improvement in cell proliferation and vitality, while expressing some typical tendon markers and anti-inflammatory cytokines;
- enhanced functional activities of ruptured tendon-derived tenocytes *in vitro* (relatively to proliferation and migration), with possible influence on tendon healing *in vivo:*

Thanks to a physiological-like mechanism of ESWT emulating E.S.A.F. action (Endothelial Stimulating Angiogenetic Factor), a peptide that perforate the endothelial capillary membrane promoting neo-angiogenesis thanks to endothelial cells migration in the interstitial space [100]. This means that the anti-inflammatory response, observing after treatment, is due to the intense circulatory washout, in the target area, causing the removal of quinine and histamine-like molecules activities and substance P present in the inflammation reaction. Another biological explanation for the analgesic effect of ESWT is related to

degeneration of the nerve fibers originating from the small neurons immune-reactive to ATF3 (Activating Transcription Factor 3), a protein linked to the activation of genes related to protein coding pro-inflammatory, which seems to derive a reduction in pain. Peripheral destruction of non-myelin fibers deputed to control of the release of the release of calcitonin gene-related peptide (CGRP) [101] and substance P determines the resolution of symptoms in the following weeks [102].

These basic science data suggest that in the field of tendinopathies, SW can be considered not only as a "palliative" therapy but rather a real curative treatment, able to relieve pain and inflammation at short-medium term follow-up but also to positively interfere with tendon structure and physiology (potential trophic effect at long term follow-up) [53]. The effects of ESWT studied in non-pathological tenocytes highlight the increase of growth and cell proliferation associated with the type I collagen deposition [103], on the pathological tenocytes is observed, in addition to the two already mentioned phenomena, the decrease in the expression of matrix metalloproteases and interleukins [104].

Studies available in scientific literature confirm that ESWT is a promoting tissue regeneration agent due to the increased turnover of collagen (restoring type I collagen) [105, 106], the increase of vascularization in myotendinous junction associated with a restore of physiological percent of elastin. In wound healing ESWT determine reduction of wound area and the increase of vascularization of the wound bed with a proliferation of granulation tissue [107, 108]. The pathogenesis process associated with degenerative tendon pathologies is related to the alteration of the mechanisms of adaptation to the mechanical and metabolic stress, with imbalance between the synthesis and degradation of collagen and extracellular matrix [109]. The remodeling phase is essential in response to repetitive micro trauma; this endogenous repair mechanism is performed by tenocytes that maintain homeostasis between the production and the degradation of collagen fibers and matrix. The remodeling is, also, related to the resistance of the tendon as a response to training, which represents a mechanical stress, thus prevents the partial or complete rupture. During the remodelling phase, it determines an increase in the mass tendon in cross section.

The remodeling phase adjustment occurs through the MMP expression [110]. Studies of tendon injuries in rats have shown the important role of MMPs in the synthesis of collagen modulation and conversion of type III collagen in type I collagen (MMP-9 and MMP-13) with extracellular matrix remodeling and healing (MMP-2, MMP-3 and MMP-14) [111].

With regard to chronic wounds, the mechanism linked to the non-healing, is associated to an alteration of the inflammatory state [112]. Physiologically phase of inflammation is related to the release of growth factors and cytokines from platelets, polymorph nuclear leukocytes, macrophages and other inflammatory cells that induce vasodilation, angiogenesis with activation of fibroblasts and tenocytes, collagen proliferation. A pathological extension of inflammation slows down the healing process[113].

Nitric oxide is a radical with a short half-life but with many biological actions, in fact possesses a bactericidal action, can induce programmed cell death of inflammatory cells, is the most potent inducer of vasodilatation and neo-angiogenesis [114, 115] favoring thus healing. The synthesis of NO takes place from the L-arginine by the enzyme NO synthase (NOS). It is observed that the levels of NOS have a peak during the week following a damage tendon and they are stable up to the 14^{th} day. Furthermore, the inhibition of NOS production determines not only a delayed healing but also an alteration of the tendinous section with less resistance and risk of rupture [107,108]. There are three NOS isoforms encoded by different genes: endothelial NOS (eNOS or type 3), neuronal NOS (nNOS or type 1), inducible NOS (iNOS or type 2) is not normally expressed but is induced by endotoxins and inflammatory mediators (lipopolysaccharide, cytokines) [117].

The levels of neuronal NOS (nNOS or type 1) coincides with the formation of small nerve fibers in animal models of tendon injury between 2 and 6 weeks [118]. These nerve fibers are the expression of the reparative phenomenon; they provide neuropeptides that act as second messengers in the complex of the tendon healing process [118]. Involved in this phenomenon are substance P and CGRP molecules released in the inflammatory stage and which cause vasodilatation and extravasation of proteins [119, 120]. ESWT Determines peripheral destruction of non-myelinic fibers deputed to control of the release of substance P determines the resolution of symptoms in the Following weeks; in some experimental protocols after 4-6 weeks from the treatment there was a significant reduction in pain symptomatology [121].

Berta *et al:*, [122] showed that, the ESWT applied at low-to medium-energy, on healthy fibroblasts in suspension, increase fibroblastic growth rate, enhance gene expression for TGF-β1 and type I and III collagen, the main factors involved in the process of repair and cell proliferation according to earlier work by Wang *et al:*, [123, 124] and Martini *et al:*, [125].

Number of pulses influences proliferation of fibroblasts, as well as the intensity of energy applied, in laboratory studies, they had a destructive dose-dependent effect

on cells in suspension, as they had a stimulating effect on dose-dependent cell proliferation. The increase in the rate of proliferation is observed in the treated cells and the greatest increase is observed from the 6th to the 12th day. The authors conclude that the parameters which should be used to stimulate the reparative processes of the tendon are 0,22 mJ/mm^2 with 1,000 pulses with a piezoelectric device, in order to obtain a proliferative stimulus for fibroblasts. In addition, the expression of TGF-β1 mRNA of fibroblasts is greater at 9 days compared to 6 days, in particular the expression of the mRNA for the type I and III collagen in a different way, at day 6 for collagen type I and 9 days for type III collagen [126]. The fibroblast growth times are in agreement with those reported in the literature for TGF-β1 and collagen types I and III demonstrating the important role of collagen in reparative differentiation processes.

Other studies investigate the effect of ESWT on biochemical and biomechanical properties of Achilles tendons. They evaluated a single session of ESWT at 0.16 mJ/mm^2 density at different number of pulses demonstrating that a low number of pulses (200) leads to an improvement of biomechanical and biochemical characteristics after 12 sessions, while high numbers of pulses (between 500 and 1000) have inhibitory effects. After 6 weeks, tenocytes express high levels of PCNA (Proliferating Cell Nuclear Antigen) expression of a reactivation of the cell cycle so of mitosis. Furthermore, it is observed an increased expression of TGF-β1, which is associated with the aggregation of the hypertrophied cells and new tendon tissue, and IGF-1 for all the reparative period [99].

Tsai *et al:*, [127] confirm the stimulating effect of ESWT on the tendon cell proliferation, in rats after tendon injury. The proliferative effect, according to this author, appears to be greater in degenerative tendon rather than in inflammatory phases where the reactive component prevails [128]. This is supported by other data in the literature [129, 130]. The comparability of approaches is not homogeneous because not all studies have applied the use of ESWT according to degenerative or inflammatory characteristics of tendinopathy.

Overall, in literature, positive results are reported for tendinitis of the rotator cuff, jumper's knee, Achilles tendinopathy, plantar fasciitis (from 60 to 91%), and lateral epicondylitis (more than 60%); only 27% for the medial epicondylitis [1 - 3]. Other tendinopathies can be treated with ESWT as trochanteric pain syndrome [131], chronic proximal hamstring tendinopathy [132] and medial tibial stress syndrome [133, 134].

Comparison of some alternative therapeutic procedures with SW would underline the efficacy of this mechanotherapy and mechanostrasduction. Ozturan *et al:* compared the short-, medium-, and long-term effects of corticosteroid injection,

autologous blood injection, and ESWT for lateral epicondylitis. Corticosteroid injection seemed to achieve a high success rate in the short-term follow-up, while autologous blood injection and ESWT resulted in better long-term results, especially considering the high recurrence percentage after corticosteroid injection. They describe a success rate of 50% of corticosteroid injection therapy, 83.3% of autologous blood injection and 89.9% of ESWT [135].

According to some other studies relatively to specific tendinopathies, not only ESWT revealed to be a noninvasive tool, useful for reducing the necessity of surgical interventions [136], but also a valid treatment option for all patients, when local steroid injection is ineffective or contraindicated [137].

CLINICAL APPLICATIONS

SW And Bone

Besides, tendinopathies, the second most representative clinical field where ESWT acts as vibratory mechanotherapy is among one of the bone healing disorders and bone vascular diseases.

First scientific evidence, of the efficacy of ESWT in improving osteogenesis in bone healing disturbances, was published in 1991 by Valchanov and Michailov, who reported positive results in 70 out of 82 patients affected by delayed or chronic bone nonunion at different sites [37]. This work can be considered a real milestone, as, until that time, the only therapeutic option for all these disturbances was surgery. Thereafter the therapeutic perspectives and scenario began to change: basic science studies and clinical trials were published in the following years, in order to explain the effects and mechanisms of action of ESWT in non-unions and delayed unions of bone fractures, reporting promising results with a success rate ranging from 50 to 85% [4, 5, 37, 138 - 140].

Another interesting field of SW application in bone healing disturbances is represented by stress fractures. Due to an altered biomechanical environment (repeated strains and overload), eventually sustained by an abnormal anatomical conformation (especially in the foot), there is an imbalance in local bone turnover, with a prevailing resorption phase, that, as a final results, if not properly and early treated, can result in a real fracture besides persisting and sometimes worsening pain,. ESWT application, in association with some other prescriptions (mainly rest and not weight-bearing), turns out to be a good strategy for accelerating bone healing and pain relief, thus allowing a more rapid return to sport and daily activities [141].

From a general point of view, bone can be considered a tissue where mechano-biological pathways are better expressed in their different forms: this in partly due to its mechanosensitivity and its complexity at the tissutal and physiologic level. Basic researches, in fact, would demonstrate that mechanical stimulation can act on the bone at different levels: surely SW action is exerted on bone, periosteal cells and their precursors, bone microvessels, and in the cross-talk between osteoblasts and osteoclasts as well [61, 142, 143].

Low-risk stress fractures in athletes usually can successfully be treated conservatively, but up to one third of them may not respond, and develope high-risk stress fractures. Surgical treatment may be the final solution, but it is in any case an invasive procedure, with potential complications. ESWT has been proposed for the treatment of stress fractures, since 1999, with interesting results, without complications. After many years and studies confirming this efficacy, it has been recently recommended that SW should be the primary standard of care in low risk patients with stress fracture and poor response to conventional treatments [141].

From a general point of view, all the following effects have been described in bone after SW exposure:

- osteogenic cells differentiation from mesenchymal precursors [62];
- direct stimulation of osteoblasts/periosteal cells [125, 144 - 148];
- orthotopic bone regeneration through stimulation of the periosteum [60];
- reduction of osteoclasts activity, through inhibition of pro-osteoclastogenic factors [61].
- accelerated migration of osteoblasts [149];
- early expression of angiogenesis-related growth factors, endothelial NOS, VEGF [143].

SW and Muscle Disorders

Spasticity: As anticipated, since the original description presented by Lohse-Busch, in 1997 [20], SW can be considered a valid therapeutic tool also in the field of spasticity and related syndromes, in children and adults, both for upper and lower limbs, although further standardization of treatment protocols (including treatment intervals and intensities) needs to be established and long-term follow-up studies are needed [21].

Interestingly, as mechanotherapies, both focal and radial SW seem to be effective in reducing spastic signs and symptoms of different origins, although the mechanisms of action are still under study and described only as hypothesis, as, all instrumental studies, until now, indeed did not reveal particular alterations or

variations in peripheral neurophysiologic activities [150].

For example, it has been described that ESWT enhances the effect of botulinum toxin type A than better than electrical stimulation, probably by modulating rheology of the muscle and neurotransmission at the neuromuscular junction [151]. Furthermore, it has been postulated that the application of SW on muscles induced a transient dysfunction of nerve conduction at the neuromuscular junctions, but surely further studies have to be performed, in order to confirm and study this possible mechanism in more details [152].

More recently, some authors began and proposed some experimental studies in humans, based on SW transcranial stimulation, that is directed to the central nervous system, thus obtaining interesting preliminary results. Moreover, focused SW transcranial stimulations were able to stimulate vigilance in patients with unresponsive wakefulness syndrome. In addition, in this case, the precise neurophysiological effects remain to be verified by a study on clinical results. Although surely with promising perspectives, these applications have to be considered as experimental ones, thus requiring further confirmations and controlled studies [153].

Besides its effectiveness in spasticity until now, relatively few studies have been published in literature regarding SW treatment for muscle disturbances.

Myofascial pain syndrome: Some authors reported beneficial effects by applying SW also in myofascial pain syndromes and fibromyalgia, even if the exact mechanisms of action are still under study.

Some hypotheses have already been proposed in any case, as for example, a different concentration of pain related substances, enhanced angiogenesis and perfusion in ischemic tissues [154]. Moreover, mechanical stimulation of SW can be useful, according to many authors, in diagnosing and treating myofascial pain syndrome [155].

Gleitz *et al:*, [156] described in details which can be the non-invasive procedures employed in myofascial pain syndrome. In this case, combination of focal and radial SW seems to be a good strategy as medical intervention. In details, focal SW can be used for diagnosis, by evoking pain referral, immediately followed by therapy that can be carried out by radial SW.

Moreover, Moghtaderi *et al:*, in treating some cases of myofascial pain related to plantar fasciitis, concluded that by combining ESWT, both for plantar fasciitis and gastrocnemius-soleus trigger points, it is possible to obtain better results [157]. Preliminary results are surely very encouraging, but further studies and a

standardization of the treatment protocol are needed as well, for optimizing therapy and results.

Myositis ossificans: Myositis ossificans, as a sequela of a direct trauma or secondary to repeated micro-injuries, can be considered a fairly common complication in sport activity. This pathologic condition is critical from the therapeutic point of view, as, in clinical practice, common "physical therapies" lack evidence. On the other hand, surgical removal, as an invasive and demolitive procedure, has to be considered the last resource, because it is frequently associated with a significative functional impairment. Relatively few articles have been published in literature about the treatment of post-traumatic myositis ossificans, and fewer about ESWT effects [158, 159].

From a general point of view, although further studies and researches are needed, preliminary experiences seem to suggest that SWs represent an interesting therapeutic tool for improving and partially restoring muscle functions and extensibility. Moreover, clinical positive results, in this disorder, can be even more evident, by associating ESWT to classical rehabilitation procedures, also by considering that this vibratory mechanotherapy is safe, economic and has no side effects; in other words, a good alternative to surgery [160].

Another revolutionary and recent field of application for ESWT is represented by regenerative medicine, especially in wound care management, where this mechanotherapy can be applied, together with some other therapeutic tools that represent a standard of care. As already described for the mechanisms of action, SW can induce tissue regeneration, in virtue of their angiogenetic potential and stem cells stimulation. Through a series of experimental and clinical studies, besides *in vitro* researches, it has been possible to enlarge its field of action to wide categories of regenerative disturbances; for example, wounds of different origin and ulcers that do not heal, as well as painful scars, diabetic ulcers, burns and some other similar disturbances [14 - 16, 18, 19].

Always recently, aiming to the angiogenic effect and trophic stimulation exerted by SW, we assisted to a growing interest and diffusion of this therapy in some andrological fields, namely *induratio penis plastica* (La Peyronie's disease) and erectile dysfunctions. From this point of view, nowadays, we can consider rapid experimental phase, already being involved in clinical practice [22 - 28].

Moreover, as anticipated, already since many years, many scientists all over the world, both in animals and in humans, as well as *in vitro*, are studying possible applications in cardiology, in order to regenerate ischaemic myocardium. This shows new interesting perspectives, in limiting hypoxic damage soon after noxious and increasing myocardial performance in the follow-up, as well as

improving heart contraction in chronic insufficiency [29 - 32].

CONFLICT OF INTEREST

The author (editor) declares no conflict of interest, financial or otherwise.

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REFERENCES

[1] Notarnicola A, Moretti B. The biological effects of extracorporeal shock wave therapy (eswt) on tendon tissue. Muscles Ligaments Tendons J 2012; 2(1): 33-7.
[PMID: 23738271]

[2] Romeo P, Lavanga V, Pagani D, Sansone V. Extracorporeal shock wave therapy in musculoskeletal disorders: a review. Med Princ Pract 2014; 23(1): 7-13.
[http://dx.doi.org/10.1159/000355472] [PMID: 24217134]

[3] Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. J Orthop Surg 2012; 7: 11.
[http://dx.doi.org/10.1186/1749-799X-7-11] [PMID: 22433113]

[4] Schaden W, Fischer A, Sailler A. Extracorporeal shock wave therapy of nonunion or delayed osseous union. Clin Orthop Relat Res 2001; (387): 90-4.
[http://dx.doi.org/10.1097/00003086-200106000-00012] [PMID: 11400900]

[5] Cacchio A, Giordano L, Colafarina O, *et al.* Extracorporeal shock-wave therapy compared with surgery for hypertrophic long-bone nonunions. J Bone Joint Surg Am 2009; 91(11): 2589-97.
[http://dx.doi.org/10.2106/JBJS.H.00841] [PMID: 19884432]

[6] Furia JP, Rompe JD, Cacchio A, Maffulli N. Shock wave therapy as a treatment of nonunions, avascular necrosis, and delayed healing of stress fractures. Foot Ankle Clin 2010; 15(4): 651-62.
[http://dx.doi.org/10.1016/j.fcl.2010.07.002] [PMID: 21056863]

[7] Furia JP, Juliano PJ, Wade AM, Schaden W, Mittermayr R. Shock wave therapy compared with intramedullary screw fixation for nonunion of proximal fifth metatarsal metaphyseal-diaphyseal fractures. J Bone Joint Surg Am 2010; 92(4): 846-54.
[http://dx.doi.org/10.2106/JBJS.I.00653] [PMID: 20360507]

[8] Ioppolo F, Rompe JD, Furia JP, Cacchio A. Clinical application of shock wave therapy (SWT) in musculoskeletal disorders. Eur J Phys Rehabil Med 2014; 50(2): 217-30.
[PMID: 24667365]

[9] Wang CJ, Wang FS, Huang CC, Yang KD, Weng LH, Huang HY. Treatment for osteonecrosis of the femoral head: comparison of extracorporeal shock waves with core decompression and bone-grafting. J Bone Joint Surg Am 2005; 87(11): 2380-7.
[PMID: 16264111]

[10] Alves EM, Angrisani AT, Santiago MB. The use of extracorporeal shock waves in the treatment of osteonecrosis of the femoral head: a systematic review. Clin Rheumatol 2009; 28(11): 1247-51.
[http://dx.doi.org/10.1007/s10067-009-1231-y] [PMID: 19609482]

[11] DAgostino C, Romeo P, Amelio E, Sansone V. Effectiveness of ESWT in the treatment of Kienböcks disease. Ultrasound Med Biol 2011; 37(9): 1452-6.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2011.06.003] [PMID: 21767905]

[12] Vulpiani MC, Vetrano M, Trischitta D, *et al.* Extracorporeal shock wave therapy in early osteonecrosis of the femoral head: prospective clinical study with long-term follow-up. Arch Orthop Trauma Surg 2012; 132(4): 499-508.
[http://dx.doi.org/10.1007/s00402-011-1444-9] [PMID: 22228278]

[13] dAgostino C, Romeo P, Lavanga V, Pisani S, Sansone V. Effectiveness of extracorporeal shock wave therapy in bone marrow edema syndrome of the hip. Rheumatol Int 2014; 34(11): 1513-8.
[http://dx.doi.org/10.1007/s00296-014-2991-5] [PMID: 24658812]

[14] Saggini R, Figus A, Troccola A, Cocco V, Saggini A, Scuderi N. Extracorporeal shock wave therapy for management of chronic ulcers in the lower extremities. Ultrasound Med Biol 2008; 34(8): 1261-71.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2008.01.010] [PMID: 18394777]

[15] Arnó A, García O, Hernán I, Sancho J, Acosta A, Barret JP. Extracorporeal shock waves, a new non-surgical method to treat severe burns. Burns 2010; 36(6): 844-9.
[http://dx.doi.org/10.1016/j.burns.2009.11.012] [PMID: 20071091]

[16] Qureshi AA, Ross KM, Ogawa R, Orgill DP. Shock wave therapy in wound healing. Plast Reconstr Surg 2011; 128(6): 721e-7e.
[http://dx.doi.org/10.1097/PRS.0b013e318230c7d1] [PMID: 21841528]

[17] Romeo P, dAgostino MC, Lazzerini A, Sansone VC. Extracorporeal shock wave therapy in pillar pain after carpal tunnel release: a preliminary study. Ultrasound Med Biol 2011; 37(10): 1603-8.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2011.07.002] [PMID: 21856074]

[18] Fioramonti P, Cigna E, Onesti MG, Fino P, Fallico N, Scuderi N. Extracorporeal shock wave therapy for the management of burn scars. Dermatol Surg 2012; 38(5): 778-82.
[http://dx.doi.org/10.1111/j.1524-4725.2012.02355.x] [PMID: 22335776]

[19] Mittermayr R, Antonic V, Hartinger J, *et al.* Extracorporeal shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy. Wound Repair Regen 2012; 20(4): 456-65.
[PMID: 22642362]

[20] Lohse-Busch H, Kraemer M, Reime U. A pilot investigation into the effects of extracorporeal shock waves on muscular dysfunction in children with spastic movement disorders. Schmerz 1997; 11(2): 108-12.
[http://dx.doi.org/10.1007/s004820050071] [PMID: 12799827]

[21] Lee JY, Kim SN, Lee IS, Jung H, Lee KS, Koh SE. Effects of extracorporeal shock wave therapy on spasticity in patients after brain injury: A meta-analysis. J Phys Ther Sci 2014; 26(10): 1641-7.
[http://dx.doi.org/10.1589/jpts.26.1641] [PMID: 25364134]

[22] Chung E, Cartmill R. Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. BJU Int 2015; 115 (Suppl. 5): 46-9.
[http://dx.doi.org/10.1111/bju.13035] [PMID: 25828173]

[23] Bechara A, Casabé A, De Bonis W, Nazar J. [Effectiveness of low-intensity extracorporeal shock wave therapy on patients with Erectile Dysfunction (ED) who have failed to respond to PDE5i therapy. A pilot study]. Arch Esp Urol 2015; 68(2): 152-60.
[PMID: 25774822]

[24] Abu-Ghanem Y, Kitrey ND, Gruenwald I, Appel B, Vardi Y. Penile low-intensity shock wave therapy: a promising novel modality for erectile dysfunction. Korean J Urol 2014; 55(5): 295-9.
[http://dx.doi.org/10.4111/kju.2014.55.5.295] [PMID: 24868332]

[25] Lei H, Liu J, Li H, *et al.* Low-intensity shock wave therapy and its application to erectile dysfunction. World J Mens Health 2013; 31(3): 208-14.
[http://dx.doi.org/10.5534/wjmh.2013.31.3.208] [PMID: 24459653]

[26] Gruenwald I, Appel B, Kitrey ND, Vardi Y. Shockwave treatment of erectile dysfunction. Ther Adv Urol 2013; 5(2): 95-9.
[http://dx.doi.org/10.1177/1756287212470696] [PMID: 23554844]

[27] Paulis G, Brancato T. Inflammatory mechanisms and oxidative stress in Peyronies disease: therapeutic rationale and related emerging treatment strategies. Inflamm Allergy Drug Targets 2012; 11(1): 48-57.
[http://dx.doi.org/10.2174/187152812798889321] [PMID: 22309083]

[28] Gruenwald I, Appel B, Vardi Y. Low-intensity extracorporeal shock wave therapy a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med 2012; 9(1): 259-64.
[http://dx.doi.org/10.1111/j.1743-6109.2011.02498.x] [PMID: 22008059]

[29] Holfeld J, Tepeköylü C, Blunder S, *et al.* Low energy shock wave therapy induces angiogenesis in acute hind-limb ischemia via VEGF receptor 2 phosphorylation. PLoS One 2014; 9(8): e103982.
[http://dx.doi.org/10.1371/journal.pone.0103982] [PMID: 25093816]

[30] Tepeköylü C, Lobenwein D, Blunder S, *et al.* Alteration of inflammatory response by shock wave therapy leads to reduced calcification of decellularized aortic xenografts in mice. Eur J Cardiothorac Surg 2015; 47(3): e80-90.
[http://dx.doi.org/10.1093/ejcts/ezu428] [PMID: 25422292]

[31] Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy for ischemic cardiovascular disorders. Am J Cardiovasc Drugs 2011; 11(5): 295-302.
[http://dx.doi.org/10.2165/11592760-000000000-00000] [PMID: 21846155]

[32] Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy as a new and non-invasive angiogenic strategy. Tohoku J Exp Med 2009; 219(1): 1-9.
[http://dx.doi.org/10.1620/tjem.219.1] [PMID: 19713678]

[33] Haupt G. Shock waves in orthopedics. Urologe A 1997; 36(3): 233-8.
[http://dx.doi.org/10.1007/s001200050096] [PMID: 9265344]

[34] Rompe JD, Furia J, Maffulli N. Eccentric loading versus eccentric loading plus shock-wave treatment for midportion Achilles tendinopathy: a randomized controlled trial. Am J Sports Med 2009; 37(3): 463-70.
[http://dx.doi.org/10.1177/0363546508326983] [PMID: 19088057]

[35] Al-Abbad H, Simon JV. The effectiveness of extracorporeal shock wave therapy on chronic Achilles tendinopathy: a systematic review. Foot Ankle Int 2013; 34(1): 33-41.
[http://dx.doi.org/10.1177/1071100712464354] [PMID: 23386759]

[36] Shrivastava SK, Kailash . Shock wave treatment in medicine. J Biosci 2005; 30(2): 269-75.
[http://dx.doi.org/10.1007/BF02703708] [PMID: 15933416]

[37] Valchanou VD, Michailov P. High energy shock waves in the treatment of delayed and nonunion of fractures. Int Orthop 1991; 15(3): 181-4.
[http://dx.doi.org/10.1007/BF00192289] [PMID: 1743828]

[38] Huang C, Holfeld J, Schaden W, Orgill D, Ogawa R. Mechanotherapy: revisiting physical therapy and recruiting mechanobiology for a new era in medicine. Trends Mol Med 2013; 19(9): 555-64.
[http://dx.doi.org/10.1016/j.molmed.2013.05.005] [PMID: 23790684]

[39] Ueberle F. Shock wave technology. In: Siebert W, Buch M, Eds. Extracorporeal shock waves in orthopaedics. Berlin: Springer 1997; pp. 59-87.

[40] Wess O, Ueberle F, Dührssen RN, *et al.* Working group technical developments – consensus report. In: Chaussy C, Eisenberger F, Jocham D, Wilbert D, Eds. High Energy Shock Waves in Medicine. Stuttgart: Thieme 1997; pp. 59-71.

[41] Gerdesmeyer L, Henne M, Göbel M, Diehl P. Physical principles and generation of shockwaves. Extracorporeal shock wave therapy: Clinical results, technologies, basics. Towson: Data Trace Publishing Company 2006; pp. 11-20.

[42] Speed C. A systematic review of shockwave therapies in soft tissue conditions: focusing on the evidence. Br J Sports Med 2014; 48(21): 1538-42.
[http://dx.doi.org/10.1136/bjsports-2012-091961] [PMID: 23918444]

[43] Gerdesmeyer L, Maier M, Haake M, Schmitz C. Physical-technical principles of extracorporeal shockwave therapy (ESWT). Orthopade 2002; 31(7): 610-7.
[http://dx.doi.org/10.1007/s00132-002-0319-8] [PMID: 12219657]

[44] Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. Clin Orthop Relat Res 2001; (387): 8-17.
[http://dx.doi.org/10.1097/00003086-200106000-00003] [PMID: 11400898]

[45] Bosco V, Buselli P. Proprietà fisiche delle onde d'urto. In: Moretti B, Amelio E, Notarnicola A, Eds. Le onde d'urto nella pratica medica. Bari: WIP Edizioni 2010; pp. 19-39.

[46] Wang CJ, Yang KD, Wang FS, Hsu CC, Chen HH. Shock wave treatment shows dose-dependent enhancement of bone mass and bone strength after fracture of the femur. Bone 2004; 34(1): 225-30.
[http://dx.doi.org/10.1016/j.bone.2003.08.005] [PMID: 14751581]

[47] Moretti B, Notarnicola A. Le onde radiali. In: Moretti B, Amelio E, Notarnicola A, Eds. Le onde d'urto nella pratica medica. Bari: WIP Edizioni 2010; pp. 15-7.

[48] Melegati G, Tornese D, Bandi M, Rubini M. Comparison of two ultrasonographic localization techniques for the treatment of lateral epicondylitis with extracorporeal shock wave therapy: a randomized study. Clin Rehabil 2004; 18(4): 366-70.
[http://dx.doi.org/10.1191/0269215504cr762oa] [PMID: 15180119]

[49] Pettrone FA, McCall BR. Extracorporeal shock wave therapy without local anesthesia for chronic lateral epicondylitis. J Bone Joint Surg Am 2005; 87(6): 1297-304.
[PMID: 15930540]

[50] Wang CJ, Chen HS. Shock wave therapy for patients with lateral epicondylitis of the elbow: a one- to two-year follow-up study. Am J Sports Med 2002; 30(3): 422-5.
[PMID: 12016085]

[51] Furia JP. Safety and efficacy of extracorporeal shock wave therapy for chronic lateral epicondylitis. Am J Orthop 2005; 34(1): 13-9.
[PMID: 15707134]

[52] Ko JY, Chen HS, Chen LM. Treatment of lateral epicondylitis of the elbow with shock waves. Clin Orthop Relat Res 2001; (387): 60-7.
[http://dx.doi.org/10.1097/00003086-200106000-00008] [PMID: 11400895]

[53] D'Agostino MC, Amelio E, Frairia R. Evoluzione delle onde d'urto – Apporto scientifico dell'Italia. Meccanismi d'azione della terapia. In: Moretti B, Amelio E, Notarnicola A, Eds. Le onde d'urto nella pratica medica. Bari: WIP Edizioni 2010; pp. 41-84.

[54] Tara S, Miyamoto M, Takagi G, *et al.* Low-energy extracorporeal shock wave therapy improves microcirculation blood flow of ischemic limbs in patients with peripheral arterial disease: pilot study. J Nippon Med Sch 2014; 81(1): 19-27.
[http://dx.doi.org/10.1272/jnms.81.19] [PMID: 24614391]

[55] Tepeköylü C, Wang FS, Kozaryn R, *et al.* Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: implications for angiogenesis and vasculogenesis. J Thorac Cardiovasc Surg 2013; 146(4): 971-8.
[http://dx.doi.org/10.1016/j.jtcvs.2013.01.017] [PMID: 23395097]

[56] Visco V, Vulpiani MC, Torrisi MR, Ferretti A, Pavan A, Vetrano M. Experimental studies on the

biological effects of extracorporeal shock wave therapy on tendon models. A review of the literature. Muscles Ligaments Tendons J 2014; 4(3): 357-61.
[PMID: 25489555]

[57] Sansone V, D Agostino MC, Bonora C, Sizzano F, De Girolamo L, Romeo P. Early angiogenic response to shock waves in a three-dimensional model of human microvascular endothelial cell culture (HMEC-1). J Biol Regul Homeost Agents 2012; 26(1): 29-37.
[PMID: 22475095]

[58] Suhr F, Delhasse Y, Bungartz G, Schmidt A, Pfannkuche K, Bloch W. Cell biological effects of mechanical stimulations generated by focused extracorporeal shock wave applications on cultured human bone marrow stromal cells. Stem Cell Res (Amst) 2013; 11(2): 951-64.
[http://dx.doi.org/10.1016/j.scr.2013.05.010] [PMID: 23880536]

[59] Raabe O, Shell K, Goessl A, *et al.* Effect of extracorporeal shock wave on proliferation and differentiation of equine adipose tissue-derived mesenchymal stem cells *in vitro:* Am J Stem Cells 2013; 2(1): 62-73.
[PMID: 23671817]

[60] Kearney CJ, Hsu HP, Spector M. The use of extracorporeal shock wave-stimulated periosteal cells for orthotopic bone generation. Tissue Eng Part A 2012; 18(13-14): 1500-8.
[http://dx.doi.org/10.1089/ten.tea.2011.0573] [PMID: 22519654]

[61] Tamma R, dellEndice S, Notarnicola A, *et al.* Extracorporeal shock waves stimulate osteoblast activities. Ultrasound Med Biol 2009; 35(12): 2093-100.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2009.05.022] [PMID: 19679388]

[62] Hausdorf J, Sievers B, Schmitt-Sody M, Jansson V, Maier M, Mayer-Wagner S. Stimulation of bone growth factor synthesis in human osteoblasts and fibroblasts after extracorporeal shock wave application. Arch Orthop Trauma Surg 2011; 131(3): 303-9.
[http://dx.doi.org/10.1007/s00402-010-1166-4] [PMID: 20730589]

[63] Wang FS, Yang KD, Chen RF, Wang CJ, Sheen-Chen SM. Extracorporeal shock wave promotes growth and differentiation of bone-marrow stromal cells towards osteoprogenitors associated with induction of TGF-β1. J Bone Joint Surg Br 2002; 84(3): 457-61.
[http://dx.doi.org/10.1302/0301-620X.84B3.11609] [PMID: 12002511]

[64] Ciampa AR, de Prati AC, Amelio E, *et al.* Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett 2005; 579(30): 6839-45.
[http://dx.doi.org/10.1016/j.febslet.2005.11.023] [PMID: 16325181]

[65] Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett 2002; 520(1-3): 153-5.
[http://dx.doi.org/10.1016/S0014-5793(02)02807-7] [PMID: 12044888]

[66] Davis TA, Stojadinovic A, Anam K, *et al.* Extracorporeal shock wave therapy suppresses the early proinflammatory immune response to a severe cutaneous burn injury. Int Wound J 2009; 6(1): 11-21.
[http://dx.doi.org/10.1111/j.1742-481X.2008.00540.x] [PMID: 19291111]

[67] Fischer S, Mueller W, Schulte M, *et al.* Multiple extracorporeal shock wave therapy degrades capsular fibrosis after insertion of silicone implants. Ultrasound Med Biol 2015; 41(3): 781-9.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2014.10.018] [PMID: 25619782]

[68] Heine N, Prantl L, Eisenmann-Klein M. Extracorporeal shock wave treatment of capsular fibrosis after mammary augmentation - Preliminary results. J Cosmet Laser Ther 2013; 15(6): 330-3.
[http://dx.doi.org/10.3109/14764172.2012.738915] [PMID: 23384126]

[69] Holfeld J, Tepeköylü C, Kozaryn R, *et al.* Shockwave therapy differentially stimulates endothelial cells: implications on the control of inflammation *via* toll-Like receptor 3. Inflammation 2014; 37(1): 65-70.
[http://dx.doi.org/10.1007/s10753-013-9712-1] [PMID: 23948864]

[70] Alunni G, Marra S, Meynet I, *et al.* The beneficial effect of extracorporeal shockwave myocardial revascularization in patients with refractory angina. Cardiovasc Revasc Med 2015; 16(1): 6-11.
[http://dx.doi.org/10.1016/j.carrev.2014.10.011] [PMID: 25555620]

[71] Gennari M, Gambini E, Bassetti B, Capogrossi M, Pompilio G. Emerging treatment options for refractory angina pectoris: ranolazine, shock wave treatment, and cell-based therapies. Rev Cardiovasc Med 2014; 15(1): 31-7.
[PMID: 24762464]

[72] Mariotto S, de Prati AC, Cavalieri E, Amelio E, Marlinghaus E, Suzuki H. Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action. Curr Med Chem 2009; 16(19): 2366-72.
[http://dx.doi.org/10.2174/092986709788682119] [PMID: 19601786]

[73] Kuo YR, Wang CT, Wang FS, Yang KD, Chiang YC, Wang CJ. Extracorporeal shock wave treatment modulates skin fibroblast recruitment and leukocyte infiltration for enhancing extended skin-flap survival. Wound Repair Regen 2009; 17(1): 80-7.
[http://dx.doi.org/10.1111/j.1524-475X.2008.00444.x] [PMID: 19152654]

[74] Shao PL, Chiu CC, Yuen CM, *et al.* Shock wave therapy effectively attenuates inflammation in rat carotid artery following endothelial denudation by balloon catheter. Cardiology 2010; 115(2): 130-44.
[http://dx.doi.org/10.1159/000262331] [PMID: 19955748]

[75] Sukubo NG, Tibalt E, Respizzi S, Locati M, D'Agostino MC. Effect of shock waves on macrophages: A possible role in tissue regeneration and remodeling. Int J Surg 2015; 24(Pt B): 124-30.
[http://dx.doi.org/10.1016/j.ijsu.2015.07.719]

[76] Vulpiani MC, Vetrano M, Savoia V, Di Pangrazio E, Trischitta D, Ferretti A. Jumpers knee treatment with extracorporeal shock wave therapy: a long-term follow-up observational study. J Sports Med Phys Fitness 2007; 47(3): 323-8.
[PMID: 17641600]

[77] Vulpiani MC, Trischitta D, Trovato P, Vetrano M, Ferretti A. Extracorporeal shockwave therapy (ESWT) in Achilles tendinopathy. A long-term follow-up observational study. J Sports Med Phys Fitness 2009; 49(2): 171-6.
[PMID: 19528895]

[78] Saggini R, Di Stefano A, Galati V, *et al.* Long-term effectiveness of combined mechanotransduction treatment in jumper's knee. Eur J Inflamm 2012; 10(3): 483-90.
[http://dx.doi.org/10.1177/1721727X1201000324]

[79] Saggini R, Cavezza T, Di Pancrazio L, *et al.* Treatment of lesions of the rotator cuff. J Biol Regul Homeost Agents 2010; 24(4): 453-9.
[PMID: 21122285]

[80] Saggini R, Fioramonti P, Bellomo RG, *et al.* Chronic ulcers: treatment with unfocused extracorporeal shock waves. Eur J Inflamm 2013; 11(2): 499-509.
[http://dx.doi.org/10.1177/1721727X1301100219]

[81] Wang CJ, Ko JY, Chou WY, *et al.* Shockwave therapy improves anterior cruciate ligament reconstruction. J Surg Res 2014; 188(1): 110-8.
[http://dx.doi.org/10.1016/j.jss.2014.01.050] [PMID: 24560350]

[82] Saggini R, Saggini A, Spagnoli AM, *et al.* Extracorporeal shock wave therapy: An emerging treatment modality for retracting scars of the hands. Ultrasound Med Biol 2016; 42(1): 185-95.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2015.07.028] [PMID: 26454624]

[83] Battery L, Maffulli N. Inflammation in overuse tendon injuries. Sports Med Arthrosc Rev 2011; 19(3): 213-7.
[http://dx.doi.org/10.1097/JSA.0b013e31820e6a92] [PMID: 21822104]

[84] Saggini R, Carmignano SM, Buoso S, Pestelli G. La meccanotrasduzione e il dolore. In: Saggini R,

Buoso S, Pestelli G, Eds. Dolore e Riabilitazione. Torino: Edizioni. Minerva Med 2014; pp. 85-91.

[85] Richardson JD, Vasko MR. Cellular mechanisms of neurogenic inflammation. J Pharmacol Exp Ther 2002; 302(3): 839-45.
[http://dx.doi.org/10.1124/jpet.102.032797] [PMID: 12183638]

[86] Schepsis AA, Leach RE, Gorzyca J. Plantar fasciitis. Etiology, treatment, surgical results, and review of the literature. Clin Orthop Relat Res 1991; (266): 185-96.
[PMID: 2019049]

[87] Roetert EP, Brody H, Dillman CJ, Groppel JL, Schultheis JM. The biomechanics of tennis elbow. An integrated approach. Clin Sports Med 1995; 14(1): 47-57.
[PMID: 7712557]

[88] Uchio Y, Ochi M, Ryoke K, Sakai Y, Ito Y, Kuwata S. Expression of neuropeptides and cytokines at the extensor carpi radialis brevis muscle origin. J Shoulder Elbow Surg 2002; 11(6): 570-5.
[http://dx.doi.org/10.1067/mse.2002.126769] [PMID: 12469081]

[89] Sems A, Dimeff R, Iannotti JP. Extracorporeal shock wave therapy in the treatment of chronic tendinopathies. J Am Acad Orthop Surg 2006; 14(4): 195-204.
[http://dx.doi.org/10.5435/00124635-200604000-00001] [PMID: 16585361]

[90] Rompe JD, Maffulli N. Repetitive shock wave therapy for lateral elbow tendinopathy (tennis elbow): a systematic and qualitative analysis. Br Med Bull 2007; 83: 355-78.
[http://dx.doi.org/10.1093/bmb/ldm019] [PMID: 17626054]

[91] Dingemanse R, Randsdorp M, Koes BW, Huisstede BM. Evidence for the effectiveness of electrophysical modalities for treatment of medial and lateral epicondylitis: a systematic review. Br J Sports Med 2014; 48(12): 957-65.
[http://dx.doi.org/10.1136/bjsports-2012-091513] [PMID: 23335238]

[92] Rompe JD, Theis C, Maffulli N. Shock wave treatment for tennis elbow. Orthopade 2005; 34(6): 567-70.
[http://dx.doi.org/10.1007/s00132-005-0805-x] [PMID: 15886855]

[93] Wang CJ. An overview of shock wave therapy in musculoskeletal disorders. Chang Gung Med J 2003; 26(4): 220-32.
[PMID: 12846521]

[94] de Girolamo L, Stanco D, Galliera E, *et al.* Soft-focused extracorporeal shock waves increase the expression of tendon-specific markers and the release of anti-inflammatory cytokines in an adherent culture model of primary human tendon cells. Ultrasound Med Biol 2014; 40(6): 1204-15.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2013.12.003] [PMID: 24631378]

[95] Leone L, Vetrano M, Ranieri D, *et al.* Extracorporeal Shock Wave Treatment (ESWT) improves *in vitro* functional activities of ruptured human tendon-derived tenocytes. PLoS One 2012; 7(11): e49759.
[http://dx.doi.org/10.1371/journal.pone.0049759] [PMID: 23189160]

[96] Vetrano M, dAlessandro F, Torrisi MR, Ferretti A, Vulpiani MC, Visco V. Extracorporeal shock wave therapy promotes cell proliferation and collagen synthesis of primary cultured human tenocytes. Knee Surg Sports Traumatol Arthrosc 2011; 19(12): 2159-68.
[http://dx.doi.org/10.1007/s00167-011-1534-9] [PMID: 21617986]

[97] Han SH, Lee JW, Guyton GP, Parks BG, Courneya JP, Schon LC. J.Leonard Goldner Award 2008. Effect of extracorporeal shock wave therapy on cultured tenocytes. Foot Ankle Int 2009; 30(2): 93-8.
[PMID: 19254500]

[98] Chao YH, Tsuang YH, Sun JS, *et al.* Effects of shock waves on tenocyte proliferation and extracellular matrix metabolism. Ultrasound Med Biol 2008; 34(5): 841-52.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2007.11.002] [PMID: 18222032]

[99] Chen YJ, Wang CJ, Yang KD, *et al.* Extracorporeal shock waves promote healing of collagenase-

induced Achilles tendinitis and increase TGF-beta1 and IGF-I expression. J Orthop Res 2004; 22(4): 854-61.
[http://dx.doi.org/10.1016/j.orthres.2003.10.013] [PMID: 15183445]

[100] Bjordal JM, Lopes-Martins RA, Joensen J, *et al.* A systematic review with procedural assessments and meta-analysis of low level laser therapy in lateral elbow tendinopathy (tennis elbow). BMC Musculoskelet Disord 2008; 9(9): 75.
[http://dx.doi.org/10.1186/1471-2474-9-75] [PMID: 18510742]

[101] Emanet SK, Altan LI, Yurtkuran M. Investigation of the effect of GaAs laser therapy on lateral epicondylitis. Photomed Laser Surg 2010; 28(3): 397-403.
[http://dx.doi.org/10.1089/pho.2009.2555] [PMID: 19877824]

[102] Hu J, Qu J, Xu D, Zhang T, Qin L, Lu H. Combined application of low-intensity pulsed ultrasound and functional electrical stimulation accelerates bone-tendon junction healing in a rabbit model. J Orthop Res 2014; 32(2): 204-9.
[http://dx.doi.org/10.1002/jor.22505] [PMID: 24136665]

[103] Vetrano M, dAlessandro F, Torrisi MR, Ferretti A, Vulpiani MC, Visco V. Extracorporeal shock wave therapy promotes cell proliferation and collagen synthesis of primary cultured human tenocytes. Knee Surg Sports Traumatol Arthrosc 2011; 19(12): 2159-68.
[http://dx.doi.org/10.1007/s00167-011-1534-9] [PMID: 21617986]

[104] Han SH, Lee JW, Guyton GP, Parks BG, Courneya JP, Schon LC. J.Leonard Goldner Award 2008. Effect of extracorporeal shock wave therapy on cultured tenocytes. Foot Ankle Int 2009; 30(2): 93-8.
[PMID: 19254500]

[105] Bosch G, Lin YL, van Schie HT, van De Lest CH, Barneveld A, van Weeren PR. Effect of extracorporeal shock wave therapy on the biochemical composition and metabolic activity of tenocytes in normal tendinous structures in ponies. Equine Vet J 2007; 39(3): 226-31.
[http://dx.doi.org/10.2746/042516407X180408] [PMID: 17520973]

[106] Bosch G, de Mos M, van Binsbergen R, van Schie HT, van de Lest CH, van Weeren PR. The effect of focused extracorporeal shock wave therapy on collagen matrix and gene expression in normal tendons and ligaments. Equine Vet J 2009; 41(4): 335-41.
[http://dx.doi.org/10.2746/042516409X370766] [PMID: 19562893]

[107] Ito Y, Ito K, Shiroto T, *et al.* Cardiac shock wave therapy ameliorates left ventricular remodeling after myocardial ischemia-reperfusion injury in pigs *in vivo:* Coron Artery Dis 2010; 21(5): 304-11.
[http://dx.doi.org/10.1097/MCA.0b013e32833aec62] [PMID: 20617568]

[108] Kuo YR, Wang CT, Wang FS, Chiang YC, Wang CJ. Extracorporeal shock-wave therapy enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of STZ-induced diabetes. Wound Repair Regen 2009; 17(4): 522-30.
[http://dx.doi.org/10.1111/j.1524-475X.2009.00504.x] [PMID: 19614917]

[109] Leadbetter WB. Cell-matrix response in tendon injury. Clin Sports Med 1992; 11(3): 533-78.
[PMID: 1638640]

[110] Riley GP, Curry V, DeGroot J, *et al.* Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. Matrix Biol 2002; 21(2): 185-95.
[http://dx.doi.org/10.1016/S0945-053X(01)00196-2] [PMID: 11852234]

[111] Oshiro W, Lou J, Xing X, Tu Y, Manske PR. Flexor tendon healing in the rat: a histologic and gene expression study. J Hand Surg Am 2003; 28(5): 814-23.
[http://dx.doi.org/10.1016/S0363-5023(03)00366-6] [PMID: 14507513]

[112] Evans CH. Cytokines and the role they play in the healing of ligaments and tendons. Sports Med 1999; 28(2): 71-6.
[http://dx.doi.org/10.2165/00007256-199928020-00001] [PMID: 10492026]

[113] Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports

Med 2003; 33(5): 381-94.
[http://dx.doi.org/10.2165/00007256-200333050-00004] [PMID: 12696985]

[114] Evans TJ, Buttery LD, Carpenter A, Springall DR, Polak JM, Cohen J. Cytokine-treated human neutrophils contain inducible nitric oxide synthase that produces nitration of ingested bacteria. Proc Natl Acad Sci USA 1996; 93(18): 9553-8.
[http://dx.doi.org/10.1073/pnas.93.18.9553] [PMID: 8790368]

[115] Ziche M, Morbidelli L, Masini E, *et al.* Nitric oxide mediates angiogenesis *in vivo* and endothelial cell growth and migration in vitro promoted by substance P. J Clin Invest 1994; 94(5): 2036-44.
[http://dx.doi.org/10.1172/JCI117557] [PMID: 7525653]

[116] Murrell GA, Szabo C, Hannafin JA, *et al.* Modulation of tendon healing by nitric oxide. Inflamm Res 1997; 46(1): 19-27.
[http://dx.doi.org/10.1007/s000110050027] [PMID: 9117513]

[117] Lin JH, Wang MX, Wei A, Zhu W, Diwan AD, Murrell GA. Temporal expression of nitric oxide synthase isoforms in healing Achilles tendon. J Orthop Res 2001; 19(1): 136-42.
[http://dx.doi.org/10.1016/S0736-0266(00)00019-X] [PMID: 11332610]

[118] Ackermann PW. Peptidergic innervation of periarticular tissue (Thesis). Stockholm: Karolinska Institutet 2001. Thesis Institutionen för kirurgisk vetenskap / Department of Surgical Science https://openarchive.ki.se/xmlui/handle/10616/38953

[119] Nakamura-Craig M, Smith TW. Substance P and peripheral inflammatory hyperalgesia. Pain 1989; 38(1): 91-8.
[http://dx.doi.org/10.1016/0304-3959(89)90078-X] [PMID: 2476709]

[120] Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. Nature 1985; 313(5997): 54-6.
[http://dx.doi.org/10.1038/313054a0] [PMID: 3917554]

[121] Vasko MR, Campbell WB, Waite KJ. Prostaglandin E2 enhances bradykinin-stimulated release of neuropeptides from rat sensory neurons in culture. J Neurosci 1994; 14(8): 4987-97.
[PMID: 7519258]

[122] Berta L, Fazzari A, Ficco AM, Enrica PM, Catalano MG, Frairia R. Extracorporeal shock waves enhance normal fibroblast proliferation in vitro and activate mRNA expression for TGF-β1 and for collagen types I and III. Acta Orthop 2009; 80(5): 612-7.
[http://dx.doi.org/10.3109/17453670903316793] [PMID: 19916698]

[123] Wang FS, Wang CJ, Huang HJ, Chung H, Chen RF, Yang KD. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. Biochem Biophys Res Commun 2001; 287(3): 648-55.
[http://dx.doi.org/10.1006/bbrc.2001.5654] [PMID: 11563844]

[124] Wang FS, Yang KD, Chen RF, Wang CJ, Sheen-Chen SM. Extracorporeal shock wave promotes growth and differentiation of bone-marrow stromal cells towards osteoprogenitors associated with induction of TGF-β1. J Bone Joint Surg Br 2002; 84(3): 457-61.
[http://dx.doi.org/10.1302/0301-620X.84B3.11609] [PMID: 12002511]

[125] Martini L, Fini M, Giavaresi G, *et al.* Primary osteoblasts response to shock wave therapy using different parameters. Artif Cells Blood Substit Immobil Biotechnol 2003; 31(4): 449-66.
[http://dx.doi.org/10.1081/BIO-120025415] [PMID: 14672419]

[126] Chao YH, Tsuang YH, Sun JS, *et al.* Effects of shock waves on tenocyte proliferation and extracellular matrix metabolism. Ultrasound Med Biol 2008; 34(5): 841-52.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2007.11.002] [PMID: 18222032]

[127] Tsai WC, Hsu CC, Tang FT, Chou SW, Chen YJ, Pang JH. Ultrasound stimulation of tendon cell proliferation and upregulation of proliferating cell nuclear antigen. J Orthop Res 2005; 23(4): 970-6.
[http://dx.doi.org/10.1016/j.orthres.2004.11.013] [PMID: 16023014]

[128] Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res 2008; 466(7): 1539-54.
[http://dx.doi.org/10.1007/s11999-008-0260-1] [PMID: 18446422]

[129] Maier M, Schmitz C. Shock wave therapy: what really matters. Ultrasound Med Biol 2008; 34(11): 1868-9.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2008.03.016] [PMID: 18471951]

[130] Peers K. Extracorporeal shock wave therapy in chronic Achilles and patellar tendinopathy. Leuven: Leuven University Press 2003.

[131] Furia JP, Rompe JD, Maffulli N. Low-energy extracorporeal shock wave therapy as a treatment for greater trochanteric pain syndrome. Am J Sports Med 2009; 37(9): 1806-13.
[http://dx.doi.org/10.1177/0363546509333014] [PMID: 19439756]

[132] Cacchio A, Rompe JD, Furia JP, Susi P, Santilli V, De Paulis F. Shockwave therapy for the treatment of chronic proximal hamstring tendinopathy in professional athletes. Am J Sports Med 2011; 39(1): 146-53.
[http://dx.doi.org/10.1177/0363546510379324] [PMID: 20855554]

[133] Rompe JD, Cacchio A, Furia JP, Maffulli N. Low-energy extracorporeal shock wave therapy as a treatment for medial tibial stress syndrome. Am J Sports Med 2010; 38(1): 125-32.
[http://dx.doi.org/10.1177/0363546509343804] [PMID: 19776340]

[134] Winters M, Eskes M, Weir A, Moen MH, Backx FJ, Bakker EW. Treatment of medial tibial stress syndrome: a systematic review. Sports Med 2013; 43(12): 1315-33.
[http://dx.doi.org/10.1007/s40279-013-0087-0] [PMID: 23979968]

[135] Ozturan KE, Yucel I, Cakici H, Guven M, Sungur I. Autologous blood and corticosteroid injection and extracoporeal shock wave therapy in the treatment of lateral epicondylitis. Orthopedics 2010; 33(2): 84-91.
[http://dx.doi.org/10.3928/01477447-20100104-09] [PMID: 20192142]

[136] Radwan YA, ElSobhi G, Badawy WS, Reda A, Khalid S. Resistant tennis elbow: shock-wave therapy versus percutaneous tenotomy. Int Orthop 2008; 32(5): 671-7.
[http://dx.doi.org/10.1007/s00264-007-0379-9] [PMID: 17551726]

[137] Lee SS, Kang S, Park NK, *et al.* Effectiveness of initial extracorporeal shock wave therapy on the newly diagnosed lateral or medial epicondylitis. Ann Rehabil Med 2012; 36(5): 681-7.
[http://dx.doi.org/10.5535/arm.2012.36.5.681] [PMID: 23185733]

[138] Elster EA, Stojadinovic A, Forsberg J, Shawen S, Andersen RC, Schaden W. Extracorporeal shock wave therapy for nonunion of the tibia. J Orthop Trauma 2010; 24(3): 133-41.
[http://dx.doi.org/10.1097/BOT.0b013e3181b26470] [PMID: 20182248]

[139] Wang CJ, Chen HS, Chen CE, Yang KD. Treatment of nonunions of long bone fractures with shock waves. Clin Orthop Relat Res 2001; (387): 95-101.
[http://dx.doi.org/10.1097/00003086-200106000-00013] [PMID: 11400901]

[140] Rompe JD, Rosendahl T, Schöllner C, Theis C. High-energy extracorporeal shock wave treatment of nonunions. Clin Orthop Relat Res 2001; (387): 102-11.
[http://dx.doi.org/10.1097/00003086-200106000-00014] [PMID: 11400870]

[141] Leal C, D'Agostino C, Gomez-Garcia S, Fernandez A. Current concepts of shockwave therapy in stress fractures. Int J Surg 2015; 24(Pt B): 195-200.
[http://dx.doi.org/10.1016/j.ijsu.2015.07.723]

[142] Lai JP, Wang FS, Hung CM, Wang CJ, Huang CJ, Kuo YR. Extracorporeal shock wave accelerates consolidation in distraction osteogenesis of the rat mandible. J Trauma 2010; 69(5): 1252-8.
[http://dx.doi.org/10.1097/TA.0b013e3181cbc7ac] [PMID: 20404761]

[143] Ma HZ, Zeng BF, Li XL. Upregulation of VEGF in subchondral bone of necrotic femoral heads in

rabbits with use of extracorporeal shock waves. Calcif Tissue Int 2007; 81(2): 124-31.
[http://dx.doi.org/10.1007/s00223-007-9046-9] [PMID: 17629736]

[144] Martini L, Giavaresi G, Fini M, *et al.* Effect of extracorporeal shock wave therapy on osteoblastlike cells. Clin Orthop Relat Res 2003; (413): 269-80.
[http://dx.doi.org/10.1097/01.blo.0000073344.50837.cd] [PMID: 12897619]

[145] Martini L, Giavaresi G, Fini M, *et al.* Shock wave therapy as an innovative technology in skeletal disorders: study on transmembrane current in stimulated osteoblast-like cells. Int J Artif Organs 2005; 28(8): 841-7.
[PMID: 16211535]

[146] Martini L, Giavaresi G, Fini M, Borsari V, Torricelli P, Giardino R. Early effects of extracorporeal shock wave treatment on osteoblast-like cells: a comparative study between electromagnetic and electrohydraulic devices. J Trauma 2006; 61(5): 1198-206.
[http://dx.doi.org/10.1097/01.ta.0000203575.96896.34] [PMID: 17099529]

[147] Tam KF, Cheung WH, Lee KM, Qin L, Leung KS. Osteogenic effects of low-intensity pulsed ultrasound, extracorporeal shockwaves and their combination - an *in vitro* comparative study on human periosteal cells. Ultrasound Med Biol 2008; 34(12): 1957-65.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2008.06.005] [PMID: 18771844]

[148] Wang FS, Wang CJ, Huang HJ, Chung H, Chen RF, Yang KD. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. Biochem Biophys Res Commun 2001; 287(3): 648-55.
[http://dx.doi.org/10.1006/bbrc.2001.5654] [PMID: 11563844]

[149] Xu JK, Chen HJ, Li XD, *et al.* Optimal intensity shock wave promotes the adhesion and migration of rat osteoblasts via integrin β1-mediated expression of phosphorylated focal adhesion kinase. J Biol Chem 2012; 287(31): 26200-12.
[http://dx.doi.org/10.1074/jbc.M112.349811] [PMID: 22654119]

[150] Sohn MK, Cho KH, Kim YJ, Hwang SL. Spasticity and electrophysiologic changes after extracorporeal shock wave therapy on gastrocnemius. Ann Rehabil Med 2011; 35(5): 599-604.
[http://dx.doi.org/10.5535/arm.2011.35.5.599] [PMID: 22506181]

[151] Santamato A, Notarnicola A, Panza F, *et al.* SBOTE study: extracorporeal shock wave therapy versus electrical stimulation after botulinum toxin type a injection for post-stroke spasticity-a prospective randomized trial. Ultrasound Med Biol 2013; 39(2): 283-91.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.019] [PMID: 23245824]

[152] Kenmoku T, Ochiai N, Ohtori S, *et al.* Degeneration and recovery of the neuromuscular junction after application of extracorporeal shock wave therapy. J Orthop Res 2012; 30(10): 1660-5.
[http://dx.doi.org/10.1002/jor.22111] [PMID: 22457214]

[153] Lohse-Busch H, Reime U, Falland R. Symptomatic treatment of unresponsive wakefulness syndrome with transcranially focused extracorporeal shock waves. NeuroRehabilitation 2014; 35(2): 235-44.
[PMID: 24990026]

[154] Ji HM, Kim HJ, Han SJ. Extracorporeal shock wave therapy in myofascial pain syndrome of upper trapezius. Ann Rehabil Med 2012; 36(5): 675-80.
[http://dx.doi.org/10.5535/arm.2012.36.5.675] [PMID: 23185732]

[155] Jeon JH, Jung YJ, Lee JY, *et al.* The effect of extracorporeal shock wave therapy on myofascial pain syndrome. Ann Rehabil Med 2012; 36(5): 665-74.
[http://dx.doi.org/10.5535/arm.2012.36.5.665] [PMID: 23185731]

[156] Gleitz M, Hornig K. Trigger points - Diagnosis and treatment concepts with special reference to extracorporeal shockwaves. Orthopade 2012; 41(2): 113-25.
[http://dx.doi.org/10.1007/s00132-011-1860-0] [PMID: 22349369]

[157] Moghtaderi A, Khosrawi S, Dehghan F. Extracorporeal shock wave therapy of gastroc-soleus trigger

points in patients with plantar fasciitis: a randomized, placebo-controlled trial. Adv Biomed Res 2014; 3: 99.
[http://dx.doi.org/10.4103/2277-9175.129369] [PMID: 24800188]

[158] Buselli P, Coco V, Notarnicola A, *et al*. Shock waves in the treatment of post-traumatic myositis ossificans. Ultrasound Med Biol 2010; 36(3): 397-409.
[http://dx.doi.org/10.1016/j.ultrasmedbio.2009.11.007] [PMID: 20133043]

[159] Miller AE, Davis BA, Beckley OA. Bilateral and recurrent myositis ossificans in an athlete: a case report and review of treatment options. Arch Phys Med Rehabil 2006; 87(2): 286-90.
[http://dx.doi.org/10.1016/j.apmr.2005.09.002] [PMID: 16442986]

[160] Torrance DA, Degraauw C. Treatment of post-traumatic myositis ossificans of the anterior thigh with extracorporeal shock wave therapy. J Can Chiropr Assoc 2011; 55(4): 240-6.
[PMID: 22131560]