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Extracorporeal shockwave therapy as a novel and potential treatment for degenerative cartilage and bone disease: Osteoarthritis. A qualitative analysis of the literature

Qiaodan Ji [a, b], Pu Wang [a, b], Chengqi He [a, b, *]

[a] Department of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China
[b] Key Laboratory of Rehabilitation Medicine in Sichuan, Chengdu, Sichuan Province, People's Republic of China

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ABSTRACT

Osteoarthritis (OA) is characterized with pathological changes on articular cartilage and subchondral bone, with clinical symptoms of pain and motor dysfunction in affected joints. A growing number of investigations demonstrated the therapeutic effects of extracorporeal shockwave therapy (ESWT) on joints with OA. While the partial mechanisms of action are based on cellular mechanotransduction through cytoskeleton into nuclei to regulate gene expression and cause biophysical influences, the efficacy and exact mechanisms are still under exploration. At present, a summary of the evidence regarding effectiveness of ESWT on OA is not available. The purpose of this review is thus to offer an overview of ESWT in the management of OA in the aspects of cartilage, subchondral bone, pain sensation and motor function, in hopes of eliciting further multi-disciplinary scientific investigations into this promising application as an adjunct to other modalities or surgery. The optimal frequencies, impulses, energy intensity and protocols of ESWT in the management of OA continue to be elucidated. Further studies are required to reveal its exact mechanisms and biophysical effects on cells, animals and humans prior to the clinical application.

Contents

* Corresponding author. Department of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan Province, People's Republic of China.
E-mail address: hxkfhcq_03@126.com (C. He).

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1. Introduction

Extracorporeal shockwave therapy (ESWT) is a type of passive physical therapy that has been employed from use in lithotripsy to the treatment of a broad range of orthopedic settings, such as calcifying tendinitis, epicondylitis humeri radialis, pseudarthrosis, delayed-unions and non-unions of fracture (Romeo et al., 2014; Wang, 2003).

Osteoarthritis (OA) is a chronic degenerative joint disease which mostly occurs in middle-aged persons and the elderly. It entails the degradation and erosion of articular cartilage, sclerosis of subchondral bones and the formation of osteophytes (Abramson and Attur, 2009). These eventually lead to a series of clinical symptoms, such as pain, swelling and limited mobility of the affected joint, restrictions of participation and low quality of life. Osteoarthritis is the most common type of arthritis and its prevalence increases with age and more than 40% of persons aged 65 years and older suffer from knee/hip OA (Dawson et al., 2004), leading to serious social and medical problems and an enormous economic burden.

In very recent years, ESWT has been introduced in the treatment of OA and a growing number of investigations demonstrated the therapeutic effects. Considering that the pathologic changes in OA involve articular cartilage and subchondral bone alterations, it is necessary to determine possible modifying effects of therapy on the integrity of joint, including cartilage and the underlying bone. Moreover, chronic pain and functional limitations in activities of daily living (ADL) are common clinical complaints of patients with OA, many of which are partly or entirely unable to work due to pain (Sofat et al., 2011). Major goals of OA management are pain controlling, joint function improvement, and ultimately quality of life (Zhao et al., 2013). Consequently, the effects on arthritic cartilage and subchondral bone, as well as pain symptom and motor function need to be explored.

At present, a summary of the evidence regarding effectiveness of ESWT in OA is not available. The purpose of this qualitative study of literature is thus to offer an overview of ESWT in the treatment and/or management of OA, regarding its therapeutic effects on articular cartilage, subchondral bone, pain sensation and motor ability, in hopes of eliciting further multi-disciplinary scientific investigations into this promising application as an adjunct to other modalities or surgery. Besides OA, additional research into relevant bone and cartilage diseases treated by ESWT are strongly encouraged as well.

2. Physics and biological research of shock waves

2.1. Definition of a shock wave

A shock wave is a single-impulse transient acoustic wave induced by electro-hydraulic, electromagnetic, piezoelectric or pneumatic generators (Mittermayr et al., 2012). In physical terms, shock waves are a series of short and definite fluctuations of acoustic energy that transmit rapidly in three-dimensional space (Ogden et al., 2001). This kind of energy release is characterized with a sudden rise to its maximum pressure at the wave front in positive phase and a longer period to return to normal level and keep decreasing into a negative phase as illustrated in Fig. 1.

There are several primary parameters utilized to describe shock waves. Energy flux density (EFD) is defined as the energy at a specific location in the focal plane during the time of one impulse within one square millimeter (mJ/mm^2) (McClure and Dorfmüller, 2003). Pressure (bar/KV/Pa) or energy levels (low/medium/high) are also applied to determine the energy density of shockwaves. Frequency (Hz) is used to describe the number of waves in per second and the energy dose (N) is the total amount of pulses. Although there is no explicit consensus on which levels constitute high- and low-energy ESWT, an EFD of less than or equal to 0.28 mJ/mm^2 and an EFD of more than or equal to 0.6 mJ/mm^2 are generally regarded as low-energy and high-energy ESWT, respectively in medical application (Albert et al., 2007).

To be “extracorporeal” and “non-invasive”, shock waves are produced by various generators outside the subjects and focused on the treated area, which is referred as ESWT.

2.2. Physical mechanisms of action and biophysical effects of shock waves

The acoustic signals induce tissue to absorb, reflect, refract and propagate the mechanical pulsed energy. The acoustic impedance

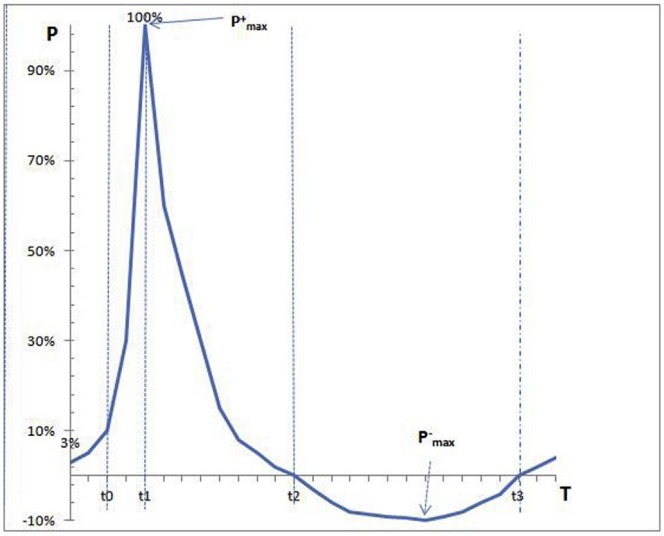

Fig. 1. The typical characteristics of a shock wave with the pressure (y axis) and time (x axis) measurements. A sudden rise of positive pressure starts at t0 and increases to the highest value (P^{+}_{max}) at the time point of t1. The time interval t1 to t2 (Zero point) is longer than that of t0 to t1. Then, it followed by a negative pulse phase from t2 to t3 during which the P^{-} can be as much as 10% of the maximum positive pressure.

varies in different tissues and can largely influence the efficacy of absorption and transmission of shockwaves. Positive pressure and the consequent negative pressure is one of the typical features of a shock wave, which cause different effects on the target tissue. A shock wave firstly evokes compression during the positive phase and then tensile force as well as shear stress in the negative phase. Tensile waves may lead to micro-bubbles of liquid molecules and exert cavitational effects on the focal area. These complex types of mechanical forces together stimulate biophysical effects on target tissues.

Until now, the whole reaction of how the tissue and cells recognize and respond to acoustic energy and convert extra stress into intercellular biological signals to reconstruct their microenvironment and regulate their behavior is still to a large extent unknown. One explanation is based on cellular mechanotransduction theory (Ingber, 2006) as illustrated briefly in Fig. 2. Shock waves, as mechanical forces, exert pressure on extracellular matrices (ECM) to cause deformation and interstitial fluid flow, and continuously alter cell cytoskeleton by stimulating sensory units in cell membrane (Vogel, 2006). Integrins are the important transmembrane proteins that connect ECM to cytoskeleton. Once activated, they aggregate in the focal adhesion sites and mediate mechanical signal transduction (Puklin-Faucher and Sheetz, 2009). The second contributors are ion channels, and their conformational alterations induced by mechanical stimuli lead to influx and efflux of ions that involve in diverse signaling pathways (e.g. MAPKs pathway, P13K-Akt-eNOS pathway etc.). Consequently, cells sense the information from membrane to nuclear component and react to various molecule changes by regulating their biophysical activities, and gene expressions for various kinds of proteins to adapt to extra mechanical stress (Ingber, 2006). Studies showed that shock waves affect transmembrane fluxes and regulate kinase (ERK) signal pathway, resulting in the possible accessibility of genomic DNA for transcription and expression to modify cell performances (Wang et al., 2002, 2004).

2.3. Therapeutic effects and present applications of shock waves

ESWT are expanding its usage from renal stones to musculoskeletal diseases. As demonstrated by Byron et al., shock waves increase cell membrane permeability and facilitate the delivery of macromolecules into cells (Byron et al., 2005). Based on cellular mechanotransduction theory, tenocytes showed intensive Proliferating Cell Nuclear Antigen (PCNA) and collagen synthesis after shockwave treatment (Chao et al., 2008). Subject to ESWT, the release of endothelial Nitric Oxide Synthase (eNOS) and Vascular Endothelial Growth Factor (VEGF) increased at the bone-tendon junction, indicating neovascularization and tissue healing (Wang et al., 2003). Transforming Growth Factor-β1 (TGF-β1) plays a crucial role in osteoneogenesis and osteoblastic lineage differentiation. Shock waves showed dose-dependent effects on osteoblasts growth and differentiation as well as the expression of TGF-β1 (Hofmann et al., 2008). The results are in agreement with the study conducted by Wang et al. In that study, significant increase of Nitric Oxide (NO), VEGF, TGF-β1 and bone morphogenetic protein 2(BMP-2) were induced by shockwave therapy in bone non-unions, which illustrate tissue proliferation and bone healing (Wang et al., 2009). As to chondrocytes, the concentration of tumor necrosis factor-alpha (TNF-α) has been inhibited by shockwave application. The decreased level of TNF-α may elucidate partial mechanisms of ESWT for chondroprotective effects and cartilage repair. Evidence supports cartilage response to ESWT with smaller denudation, enhanced density and more chondrocytes formation for osteochodritis dissecans of knee in rabbits (Lyon et al., 2013).

In all, ESWT is widely used in the applications of orthopedic settings such as tendinitis and long bone non-unions to promote connective tissue healing, skeletal and cartilaginous regeneration due to its therapeutic effects on fibroblasts, osteoblasts and chondrocytes.

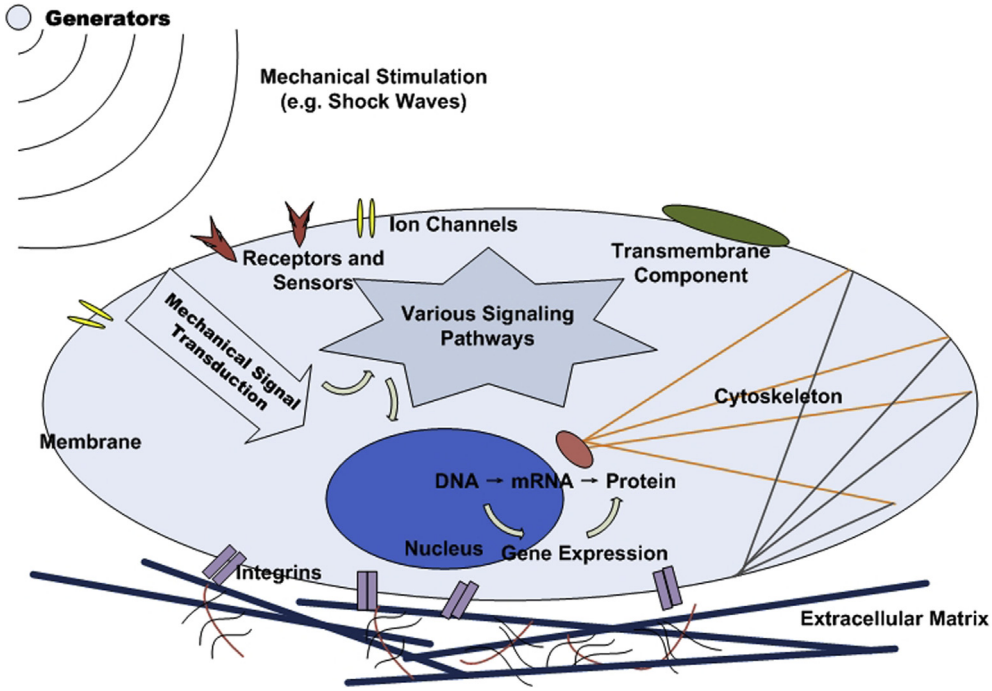

Fig. 2. The brief illustration on cellular mechanotransduction process. Mechanosensory components in cell membrane such as integrins, ion channels, various sensors and growth factor receptors are activated by mechanical forces (e.g. shock waves) which result in a series of biological events from cytoskeletal organization rearrangement to nuclear expression modulation. The process involves different molecular signal pathways to transduce mechanical signals, regulate gene and protein expressions as well as cell metabolic changes such as cell proliferation, differentiation and apoptosis at a microscale, which, in turn, exerting effects on tissue healing and regeneration at a macroscale.

3. The effects of ESWT on OA

However, up to date, the application of ESWT in the treatment of OA is nearly blank in clinical practice. The reasons probably lie in its unclear mechanisms of action and the lack of scientific evidence. OA is characterized with pathological changes on articular cartilage and its underlying subchondral bone. Moreover, most patients bitterly complain about joint pain and activity limitations clinically (Fig. 3). In all, ideal therapeutic modalities are required to have the effectiveness and efficacy on clinical symptoms to ameliorate pain, enhance functional activities and ultimately improve life quality of individuals with OA. Dealing with the complaints which patients have and meeting their practical needs in daily living are the fundamental aspects in the medical concerns. Recently, there is a tendency towards investigating effects of ESWT on OA and a growing number of studies showed favorable results. We are here to summarize the relevant research progress of ESWT in the treatment of OA based on biological effects on articular cartilage and subchondral bone as well as improvements in clinical symptoms of pain and motor dysfunction in a qualitative and critical way. Main characteristics of these studies are listed in Table 1.

3.1. The effects of ESWT on articular cartilage

Articular cartilage deterioration is one of the main features observed in patients with OA. Distributions of abnormal force load progressively accelerate the severity of cartilage rupture in the progression of OA, which in turn induce more clinical signs for patients (Dedrick et al., 1991). Therefore the favorable turn of cartilage aimed at improving arthritic symptom must be involved in the management of osteoarthritis.

3.1.1. The histological effects on articular cartilage

Cartilage specimens are subjected to histochemical examinations to evaluate the stage and grade of cartilage lesion. Generally, with hematoxylin-eosin and safranin-O stains, evaluations are made by using Mankin score system (Mankin et al., 1971) or observing the cartilage fissuring, chondrocyte concentration, chondrocyte vitality and chondrocyte apoptosis through a microscopy. A series of studies conducted by Wang et al. illustrated the significant lower Mankin scores and safranin-O stain in the group of ESWT with identical parameters of 800 impulses at 14 KV, applied to medial proximal tibia of osteoarthritic knee induced by Anterior Cruciate Ligament Transection (ACLT) in rats (Wang et al., 2012, 2011a, 2011b). An increase in chondrocyte activity and decreases in cartilage fissuring and chondrocyte apoptosis were also observed in ESWT group when compared with the untreated group. It is worth noting that these similar results were obtained when the same single session of ESWT applied to the equal region but at different time points after ACLT surgery. Rats received ESWT immediately after ACLT (Wang et al., 2011b), one week after ACLT (Wang et al., 2012), and twelve weeks after ACLT (Wang et al., 2011a) presented the consistent chondroprotective effects on impaired cartilage. It makes no difference whether ESWT applied at an early stage or a later phase. The authors proposed that ESWT may have beneficial effects both in the initiation and the progression of OA in rats. Nevertheless, a paucity of quantitative statistical data comparison may hamper this conclusion. Therefore, additional studies on various time points of ESWT application are required.

Further, Wang et al. conducted another investigation to explore the effects of ESWT in rats with OA when the equal parameters as before (800 impulses at 14 KV) were adopted (Wang et al., 2013a). However, the numbers of ESWT treatments varied with one treatment once a week in group III, twice a week for 2 treatments in group IV and three times a week for 3 treatments in group V. The results of safranin-O matrix staining and Mankin score of group III and IV were significantly better than untreated group and group V, indicating that excessive bouts of ESWT treatments may cause more cartilage damage rather than the favorable promotion (Wang et al., 2013a). Consequently, more caution should be taken when an overdose of ESWT treatment is applied.

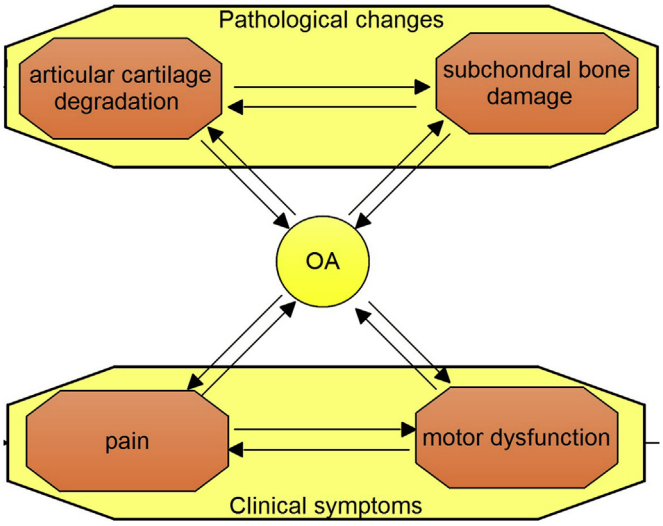

Fig. 3. Osteoarthritis (OA) is characterized with pathological changes on articular cartilage and subchondral bone, with clinical symptoms of pain and motor dysfunction in affected joints. Degenerated cartilage is associated with chronic inflammation response of joint and the acceleration of clinical symptoms severity. Abnormal bone turnover then induce an imbalanced force and pressure distributions within the knee, leading to the damage of cartilage over the tough surface of subchondral bone. When related to clinical symptoms, most patients go to clinics for the sake of pain relief and motor function improvements. The pathological changes and clinical symptoms have interactions with each other to form a vicious circle, accelerating the progress of OA development.

3.1.2. The immunohistochemical effects on articular cartilage

Type II collagen of cartilage or urinary concentration of C-telopeptide of type II collagen (CTX-II) and matrix metalloproteinase (MMP) are common markers of cartilage and matrix degradation utilized in immunohistochemical examinations, combined with additional indexes of glycosaminoglycan (GAG) concentration, cartilage oligomeric protein (COMP) expression and many others. Type II collagen is a basic component part of cartilage. And its degeneration leads to augmented fragments of CTX-II which were detected in patients with OA condition (Garnero et al., 2001). MMPs associated with cartilage catabolism, degrades collagen II in cartilage and is involved in OA development (Vincenti and Brinckerhoff, 2002). Application of ESWT resulted in the decline of CTX-II concentration and MMP expression of knee OA in rats (Wang et al., 2011a, 2011b, 2012, 2013a).

Moreover, a recent study conducted by Wang P and colleagues utilized rabbit OA model to investigate the effects of ESWT (Energy intensity: 1.6 bar; Frequency: 5 Hz; Pulses: 1200) on cartilage of distal femoral condyle and proximal tibia condyle (Wang et al., 2014). The results showed the significant decrease of MMP-1 and MMP-3 levels in ESWT-treat group compared with ACLT group. While a lack of blank control group in this study may provide no baseline levels, which makes it difficult to compare the normal condition with the ESWT group (Wang et al., 2014). Therefore, the conclusion that shock waves have cartilage protective effects may not be drawn so early. However, the alterations of cartilage metabolism did exist after shock waves stimulation.

Another investigation showed reductions of interleukin-10 (IL-

Table 1
Main characteristics of studies demonstrating beneficial effects of ESWT in OA.

Target	Aim of study	Type of machine	Frequency (Hz)	Impulses	Intensity energy levels, EFD (mJ/mm^2), pressure (bar/KV/Pa)	ESWT protocol	Primary outcomes	Reference
Male Sprague Dawley rats (8 wks)	A + S	OssaTron orthotriptor (Sanuwave, Alpharetta, GA)	NR	800	14 KV (equivalent to 0.18 −0.22 mJ/mm^2)	A single session at 12 wk after ACLT	Cartilage: ↓Safranin O stain, ↓Mankin score, ↓COMP, ↓CTX-II; Subchondral bone: ↑vWF, ↑VEGF, ↑BMP-2, ↑OCN.	Wang C et al. (2011a)
Male Sprague Dawley rats (8 wks)	A + S	OssaTron orthotriptor (Sanuwave, Alpharetta, GA)	NR	800	14 KV (equivalent to 0.18 −0.22 mJ/mm^2)	A single session immediately after ACLT	Cartilage: ↓Mankin score and Safranin O stain, ↓fissuring and apoptosis, ↑concentration and activity of chondrocyte, ↓COMP, ↓CTX-II; Subchondral bone: ↓BMD and FT, ↑trabecular bone and osteocytes, ↑OCN.	Wang C et al. (2011b)
Male Sprague Dawley rats (8 wks)	A + S	OssaTron orthotriptor (Sanuwave, Alpharetta, GA)	NR	800	14 KV (equivalent to 0.18 −0.22 mJ/mm^2)	A single session at 1 wk after ACLT	Cartilage: ↓Mankin score and Safranin O stain, ↓DKK-1 and MMP-13, ↑Wnt-5a and β-catenin; Subchondral bone: ↓DKK-1 and MMP-13, ↑Wnt-5a and β-catenin.	Wang C et al. (2013a)
Male Sprague Dawley rats (8 wks)	A + S	OssaTron orthotriptor (Sanuwave, Alpharetta, GA)	NR	800	14 KV (equivalent to 0.18 −0.22 mJ/mm^2)	A single session at 1 wk after ACLT	Cartilage: ↑proliferation, concentration and activity of chondrocyte, ↑serum type II collagen; Subchondral bone: ↑microarchitecture integrity and improved trabecular bone, ↑VEGF, BMP-2 and OCN.	Wang C et al. (2012)
Male Sprague Dawley rats (10 wks)	A + S	OssaTron orthotriptor (Sanuwave, Alpharetta, GA)	NR	800	14 KV(equivalent to 0.18 −0.22 mJ/mm^2)	At 1 wk after surgery, Group III: once/wk; Group IV: twice/wk; Group V: 3 times/wk.	Group III: ↑serum type II collagen, ↓MMP-13, improved tissue distributions of COB, CAB and FT; ↑vWF, VEGF, BMP-2 and OCN. Group IV: similar to group III. Group V: comparable with the untreated group.	Wang C et al. (2013b)
Mixed breed horses (2−3 yrs)	S	NR	NR	Day 14: 2000; Day 28: 1500	Day14:0.14 mJ/mm^2; Day 28:0.15 mJ/mm^2	Two treatments on day 14 and 28 after surgery	↑Serum OCN and concentration of CTX-I, ↑synovial fluid epitope CS846 in ESWT group; no difference on subchondral bone change both in ESWT and PSGAGT groups.	Kawcak et al. (2011)
Human arthritic and healthy chondrocytes	A	Electromagnetic generator system (MINILISH SL1, STORZ medical)	NR	A1: 500; A2:1000; B1: 500; B2: 1000	A1: 0.055 mJ/mm^2 A2: 0.055 mJ/mm^2 B1: 0.17 mJ/mm^2 B2: 0.17 mJ/mm^2	A single bout	↔β1 integrin, ↓IL-10 and TNF-alpha, and no significant decrease of cell viability both in healthy and arthritic chondrocytes.	Moretti et al. (2008)
Human arthritic and healthy osteoblasts	S		NR	A1: 500; A2:1000; B1: 500; B2: 1000		A single bout	Healthy chondrocytes: ↔CD29/β1 integrin and	Iannone et al. (2009)

(*continued on next page*)

Table 1 (*continued*)

Target	Aim of study	Type of machine	Frequency (Hz)	Impulses	Intensity energy levels, EFD (mJ/mm^2), pressure (bar/KV/Pa)	ESWT protocol	Primary outcomes	Reference
		Electromagnetic generator system (MINILISH SL1, STORZ medical)			A1: 0.055 mJ/mm^2 A2: 0.055 mJ/mm^2 B1: 0.17 mJ/mm^2 B2: 0.17 mJ/mm^2		CD105/endoglin, ↔TNF-alpha, ↑IL-10; Arthritic chondrocytes: ↑CD29/β1 integrin, CD105/endoglin and IL-10 showed in B1. The other groups showed results like the healthy ones.	
Male New Zealand rabbits (8 mons)	A	Electromagnetic generator system (SwissDolorClast, Switzerland)	NR	600	1.5×10^5 Pa	Immediately after ACLT, 3 times/wk in 1wk	↓fibrillation and erosion,↓NO, ↓chondrocyte apoptosis	Zhao et al. (2012)
New Zealand white rabbits (5 mons)	A + S	MASTERPULS MP100, STORZ MEDCAL	5	1200	1.6 bars	At 2 month after ACLT; 3 times/wk with 1 wk interval; For total 6 times in 4 wk	Cartilage: ↓Safranin O stain and erosion,↓MMP-1 and MMP-3; Subchondral bone:↓BMD, ↓trabecular bone thickness and volume	Wang P et al. (2014)
Mixed breeds dogs	M	NR	4	1500	0.1 mJ/mm^2	3 times with 3 wk interval	Dogs with ESWT had a positive trend for ↑ROM and PVF when compared to dogs in the control group with no difference.	Dahlberg et al. (2005)
Various breeds horses (10–17 yrs)	P + M	EquiTron/Versatron machine (USA)	NR	700–1500	High or maximum energy level within the tolerance	Most for twice or three times at 2–3 wks interval	↓Positive response for joint flexion due to pain, ↓lameness score and ↑functional performance in racing or full work	Revenaugh et al. (2005)
Different breeds of dogs (2–12 yrs)	M	Electro Medical Systems (Swiss DolorClast Vet)	15	2000	2 bars	3 times with 1 wk interval	↑Symmetry indices with significantly improved peak vertical force and vertical impulses of both hind-legs in the treated group	Mueller et al. (2007)
Male Sprague Dawley rats	P + M	Dornir Med Tech; Epos Germany	4	1000	0.08 mJ/mm^2	A signal bout at 10 wk after surgery	↑Walking duration extended 4,7,14 days after ESWT,↓CGRP expression in DRG neurons	Ochiai et al. (2007)
Mixed breeds horses (2–3 yrs)	P + M	NR	NR	Day 14: 2000; Day 28: 1500	Day 14:0.14 mJ/mm^2; Day 28:0.15 mJ/mm^2	Two treatments on day 14 and 28 after surgery	↓Lameness scores, ↓response of carpal flexion, ↓total protein concentration in synovial fluid	Frisbie et al. (2009)
Patients aged ≥ 45 yrs	P + M	Electro Medical Systems (Swiss DolorClast; Nyon, Switzerland)	6	4000	0.25 mJ/mm^2	Two treatments at weekly interval	↓VAS scores, improved WOMAC and Lequesne index, ↑patient perception of clinical severity of OA	Zhao et al. (2013)
Patients aged ≥ 40 yrs	P + M	Piezoelectric system (F10G4 Richard Wolf GmbH, Knittlingen, Germany)	1–8	2000	0.03–0.4 mJ/mm^2; 11–82Mpa	Six treatment, once/wk for 6 wks	Compared with isokinetic and ultrasound treatments, ESWT group showed the best effects:↓VAS score and Lequesne's index, ↑ROM and muscle peak torques	Chen et al. (2014)

A: articular cartilage; S: subchondral bone; P: pain sensation; M: motor function; ESWT: extracorporeal shock wave therapy; wk(s): week(s); mon(s): month(s); yr(s): year(s); NR: not reported; EFD: energy flux density; ACLT: anterior cruciate ligament transection; BMD: bone mineral density; CTX-II: type II collagen C- telopeptide; COMP: the cartilage oligomeric matrix protein; vWF: von Willebrand factor; VEGF: vascular endothelial growth factor; BMP-2: bone morphogenic protein 2; OCN: osteocalcin; DKK-1: Dickkopf-1; MMP: matrix metalloproteinase; FT: fibrous tissue; COB: cortical bone; CAB: cancellous bone; PSGAGT: polysulfated glycosaminoglycan treatment; IL-10: interleukin-10; TNF-alpha: tumor necrosis factor-alpha; ROM: range of motion; PVF: peak vertical force; CGRP: calcitonin gene-related peptide; DRG: dorsal root ganglia; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster University Osteoarthritis Index; ↑: increase; ↓: decrease; ↔: no change.

10) and TNF-α in osteoarthritic chondrocytes after different protocols of shock waves stimulation (EFD: 0.055 and 0.17 mJ/mm^2; Energy level: 2.5 and 5.5; Pulses: 500 and 1000) (Moretti et al., 2008). TNF-α mediates a wide range of biochemical reactions, including activation of MMPs synthesis, transcription factor NF-kappa B and chondrocyte apoptosis (Rath and Aggarwal, 1999). Inversely, the expression of the degrading cytokine TNF-α was correlated to the expression of the regulatory cytokines IL-10 (Moos et al., 1999). The authors concluded that ESWT might have chondroprotective effects by restoring the production of IL-10 and TNF-alpha by osteoarthritic chondrocyte to a normal level (Moretti et al., 2008).

A recent study demonstrated a decreased production of NO with shockwaves application of 600 impulses at 1.5 × 10^5 pa on knee joint in OA rabbits (Zhao et al., 2012). Along with many cytokines such as IL-1, IL-7, IL-10 and TNF-α, NO mediates the inflammatory response and is associated with the expression of MMPs. A decreased level of NO may result in a reduced catabolic rate of articular cartilage and induced disease-modifying effects within osteoarthritic joint. NO production, NF-Kappa B activation and the synergy or antagonism among cytokines have intricate relationships with each other (Hashimoto et al., 1998; Umezawa and Chaicharoenpong, 2002). All of them are involved in the initiation and progression of OA and modulate cartilage homeostasis through various biological pathways (Fernandes et al., 2002). The pathogenesis mechanism of OA has not been completely understood. Therefore, further explorations are needed.

3.2. The effects of ESWT on subchondral bone

OA patients suffer from subchondral bone loss in the initiation of OA and bone sclerosis later (Hayami et al., 2006). Subchondral bone stiffness can blemish the normal distribution of mechanical load within joint, making it difficult for overlying articular cartilage to buff force and pressure (Dedrick et al., 1991). As a consequence, cartilage degenerates gradually. A growing number of evidence proposed the great importance of subchondral bone in the early stage of OA followed by the damage of cartilage (Burr, 1998; Martel-Pelletier et al., 2007). Therefore, subchondral bone remodeling is supposed to be on the target list for treatment of OA.

3.2.1. The histological effects on subchondral bone

The quantity of subchondral trabecular bone and its morphology and tissue distributions, fibrous tissue and the amount of osteocytes were examined to evaluate the effects with ESWT (800 impulses at 14 KV equivalent to 0.22 mJ/mm^2) on ACLT-induced KOA rats (Wang et al., 2013a, 2012, 2011b). Lower percentage of subchondral trabecular bone was detected in OA group without shock waves. Furthermore, numbers of osteocytes significantly increased in ESWT-treated group compared with untreated ones (Wang et al., 2011b). With extracorporeal shockwaves applied to the subchondral bone of media tibia condyle, Wang C et al. have reported better tissue distributions including cortical bone, cancellous bone and fibrous tissue (Wang et al., 2012, 2013a). The authors suggested that ESWT is a potential treatment for the process of subchondral bone remodeling in OA. Taken together, these histological findings demonstrate that shock waves stimulus may be of great benefit in enhancing subchondral bone anabolism and improving trabecular microarchitecture. However, the readers should note that OA patients present increased bone turnover, which result in subchondral bone loss at first stage but sclerosis and osteophyte formation in the following stage (Dedrick et al., 1991). ESWT may be detrimental to quicken the excess bone formation leading to osteophytosis and stiffness.

An additional study showed that with ESWT, decreased subchondral trabecular bone thickness, less mineral density and reduced bone volume were found (Wang et al., 2014). Rabbits received shock waves two months after ACLT surgery and it may be in the following stage rather than the initiation of OA, during which subchondral bone stiffness and bone cysts occur instead of bone loss. ESWT may help enhance the subchondral density at first and then retard the active bone turnover. By now, the long-term effect of ESWT on the subchondral bone of OA in vitro and in vivo still remains to be elucidated.

3.2.2. The immunohistochemical effects on subchondral bone

In several investigations made by Wang C et al., 800 impulses shock waves at 14 KV applied to subchondral bone region in OA rats showed beneficial effects for bone enhancement and growth (Wang et al., 2011a, 2011b, 2012, 2013a). BMP-2 is associated with cell proliferation and extracellular matrix production, and the production of BMP-2 and osteocalcin are adequately expressed in healthy osteoblasts to maintain bones integrity and metabolism. Subjected to ESWT, rats with induced OA presented augmented BMP-2 and osteocalcin expressions compared with the untreated ones. And the results are comparable to that of the control group (Wang et al., 2013a). Moreover, significant increase of VEGF and von Willebrand factor (vWF) were observed in the group with shockwave treatment compared with the untreated (Wang et al., 2012). The authors speculated that ESWT stimulates increased vascularization and osteogenesis indicative of bone remodeling.

To evaluate molecular changes in KOA rats after ESWT, Wang et al. tended to analyze the expression of Dickkopf-1 (DKK-1), MMP-13, Winless 5a (Wnt-5a), and beta-catenin (β-catenin) in subchondral bone (Wang et al., 2013b). The wnt/beta-catenin pathway is involved in bone remodeling process and bone homeostasis maintenance (Westendorf et al., 2004). Since DKK-1 acts as an inhibitor in wnt action, the reduced DKK-1 can lead to the enhancement of bone density and trabecular bone mass (Pinzone et al., 2009). ESWT attenuated the degradation of subchondral bone by decreasing the expression of DKK-1 and MMP13 and promoting Wnt-5a and β-catenin production (Wang et al., 2013b).

Similarly, compared with administration of polysulfated glycosaminoglycan treatment (PSGAGT), a popular treatment for joint disease in horses, ESWT was more effective in facilitating the serum osteocalcin concentration (Kawcak et al., 2011). Shock waves with 2000 pulses at 0.14 mJ/mm^2 applied to eight regions on the proximal and distal aspect, and the other 400 pulses were devoted over the induced osteoarthritis fragment. Concentrations of the synovial fluid epitope CS846, a marker of aggrecan synthesis (Frisbie et al., 2008), were significantly increased in the ESWT group, with higher concentration of the C-terminal telopeptide of type I collagen compared with PSGAGT-treated group (Kawcak et al., 2011). Although histological examinations revealed no differences among placebo- and ESWT- or PSGAGT-treated horses, intervention of extracorporeal shock waves did change several biomarkers relevant to subchondral bone remodeling (Kawcak et al., 2011). Hence one can see that further time-dependant effects on subchondral bone are needed to investigate until the differences become discernible by microscopy observation.

Effects on human osteoarthritic subchondral osteoblasts and healthy ones were examined (Iannone et al., 2009). 500 or 1000 impulses at 0.55 mJ/mm^2 and 0.17 mJ/mm^2 directly applied to vial containing the cells. The test-vial was placed in a special cylindrical support on the shockwave generator system. Interestingly, IL-10 intracellular levels significantly increased in OA or healthy subchondral osteoblasts (Iannone et al., 2009), which was opposed to the down-regulation of IL-10 expression in human chondrocytes of OA utilizing the identical protocol of ESWT (Moretti et al., 2008). IL-10 acts as either inhibitor or promoter in the mediation of a broad

range of reactions. It activates functional responses for preventing osteoclastogenesis in the marrow culture system of rats (Xu et al., 1995) and promoting the growth of B cells (Rousset et al., 1992). On the other hand, IF-1 and TNF-α synthesis by monocytes are inhibited with IL-10 involvement (de Waal Malefyt et al., 1991). It's hard to confirm the role of this pleiotropic immune cytokine. IL-10 reduction in OA chondrocytes and increased IL-10 expression in osteoblasts demonstrated the dissimilar response of cartilage and subchondral bone to the administration of shock waves stimulation. More studies are encouraged to estimate the diverse function of IL-10 and its exact role played in different components within arthritic knees.

3.3. The effects of ESWT on the pain sensation

Elderly people with degenerative OA bitterly complain about chronic joint pain and motor dysfunction (Sofat et al., 2011). Suffered from moderate/severe knee ache, patients may avoid physical movement unconsciously or on purpose. Gradually, joint swelling, stiffness and functional limitations accelerate caused by protective immobilization due to pain. Despite pharmacologic treatment and non-pharmacologic treatment, most subjects with OA continue to experience pain. Therefore, alleviation of pain symptom should be the main target in the management of OA.

3.3.1. The effects on animal models

Subsequent to 1000 pulses shock waves with an EFD of 0.08 mJ/mm^2 at 4 Hz to the left medial side of the knees, OA rats showed significant less ratios of calcitonin gene-related peptide (CGRP) expressions in neurons innervating the knee joint, compared with untreated OA group (Ochiai et al., 2007). CGRP is expressed by nociceptors in dorsal root ganglia (DRG) neurons and involved in joint pain sensation (He et al., 1990). Augmented production of CGRP in DRG increases the pathological response in the chronic inflammatory knee joint (Staton et al., 2007). The authors presumed that shock waves inhibit the nerve fibers to transmit pain information by degenerating nerve endings and help to reduce the number of CGRP-immunoreactive DRG neurons, which ultimately leads to pain relief.

Moreover, Revenaugh shared several clinical experiences utilizing shock waves stimulation to treat horses with OA (Revenaugh, 2005). 5-, 20-, and 35-mm focal depth probes were usually used over the affected carpal, tarsal or metatarsal bones joints with relative high or maximum energy levels. Flexion tests of OA joints were carried out to assess the response intensity caused by pain. Moderate/severe responses to a flexion test improved to mild/moderate level following ESW treatment, and some horses even had clinical sound performance, indicating an analgesic effect of shock waves (Revenaugh, 2005). The results are in excellent agreement with the study of Frisbie's (Frisbie et al., 2009). However, what the readers should keep in mind is that case report is based on secondary data analysis instead of the original study design. Therefore, authors may have a tendency to draw an expected conclusion in favor of ESWT. However, therapeutic effects would not be ignored according to this case reports analysis.

3.3.2. The effects in clinical trials

In addition, attenuated pain after ESWT was reported in human model with OA (Chen et al., 2014; Zhao et al., 2013). Recently, four weeks of weekly ESWT treatment (Pulses: 4000; EFD: 0.25 mJ/mm^2; Frequency: 6 Hz) significantly reduced visual analogue scale (VAS) scores indicative of pain reduction compared with the placebo group (Zhao et al., 2013). Decreased scores of pain aspect in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) (McConnell et al., 2001) were showed in the group with ESWT (Zhao et al., 2013).

Focusing on the treatment of knee OA with popliteal cyamella, Chen et al. recruited patients over 40 years of age with sesamoid syndrome of osteoarthritis to investigate the clinical effects of isokinetic exercise, ultrasound treatment and shockwave therapy (Chen et al., 2014). The latter showed the greatest degree of pain reduction measured by VAS compared with the other two treatments.

3.4. The effects of ESWT on motor function

Aged patients seek clinical service for pain-related motor dysfunction (Sofat et al., 2011) (Sofat et al., 2011). Population with OA suffer from limbs disability with difficulties in standing, sauntering, walking up and down stairs and rising from or sitting on a chair (Van der Esch et al., 2007). All these functional limitations may put the individuals at risk of falls (Peat et al., 2001) and prevent the elderly from participating in daily activities and having a quality life. Accordingly, primary healthcare should include the training of muscle strength and the management of joint functional ability.

3.4.1. The effects on animal models

In Ochiai's study, the effect induced by ESW on functional performance of knee OA rats was evaluated (Ochiai et al., 2007). Walking duration was measured on an accelerating Rota-Rod Treadmill for behavioral tests. Significant longer time for walking was observed on 4, 7, and 14 days after ESWT. Interestingly, the best results appeared on day 4 after shock waves application, but restored to baseline levels after two weeks. What's more, 21 and 28 days after treatment, there was no difference between the ESWT- and placebo-treated groups (Ochiai et al., 2007). Previous study showed that ESWT caused nerve fiber degeneration, reduced the expression of CGRP in DGR neurons, and ultimately led to the analgesic effect (Ohtori et al., 2001). However, regeneration occur in fibers on 14 days after ESW, which coincides with the restoration time of walking duration (Ochiai et al., 2007). The authors proposed that nerve fibers reinnervation contributes to the pain perception, as a result rats couldn't bear too long walking time and distance because of the regained and re-increased pain. ESWT may have a time-limited effect on pain relief and functional ability enhancement. Further study is supposed to decide the peak time point of best outcomes and to evaluate the accumulative effects by applying shock waves more than once.

To investigate effects of radial shockwave therapy on the limb function of dogs with hip OA, Mueller and colleagues utilized a treadmill containing four biomechanical force sensors to analyze the peak vertical force (PFz) and vertical impulses (IFz). Symmetry indices were used to evaluate the equipotent degree between the more weight-bearing limb and the lamer limb (Mueller et al., 2007). The difference in PFz and IFz of the two limbs became not significant in 6 weeks and 3 months after ESWT, indicating a better weight distribution symmetry and improved limb function with decreased disability after shock waves application. Another study demonstrated that three treatments of ESWT had beneficial effects on the maintenance of motor function in OA dogs with stifle joint (Dahlberg et al., 2005). Peak vertical force (PVF) was assessed in platform gait analysis and goniometry was used to measure the joint range of motion (ROM) before and after treatments. Though there was no difference, ESWT has been proved to decrease lameness degree of OA dogs with a tendency to improve PVF and ROM, compared with a negative trend for continuously decreasing ROM and PVF in the untreated group (Dahlberg et al., 2005).

In the case studies of horses reported by Revenaugh (Revenaugh, 2005), the clinician assigned lameness scores (American Association of Equine Practitioners' grading scale for lameness)

for each horse before and after ESWT. The horses with arthritic carpal or tarsal joint revealed various degree of functional improvement reflected by reduced lameness scores, indicating ESWT as a useful tool for enhancing the motor performance of OA horses. Another study is in support of this finding (Frisbie et al., 2009). It demonstrated that in horses with osteoarthritic carpal joints, the degree of lameness decreased with a significant difference between ESWT- and placebo-treated horses.

3.4.2. The effects in clinical trials

Recent evidence suggests that ESWT may be an efficient and effective intervention for human patients of OA in clinical studies (Chen et al., 2014; Zhao et al., 2013). For example, in subjects over 45 years of age with Kellgren and Lawrence grade II or III OA, weekly treatment of ESWT for four weeks with parameters of 6 Hz, 0.25 mJ/mm^2 and 4000 pulses showed significant enhancement of functional ability measured by Lequesne index and WOMAC (Zhao et al., 2013). However, a paucity of objective data may cause bias in conclusion. Since patients answer questions according to their own conditions and feelings, it is necessary to draw the readers' attention to the persuasiveness of it. Therefore, more objective measurements are needed. Moreover, Chen et al. conducted a clinical trial to investigate the beneficial effects of isokinetic exercise (group I), ultrasound treatment (group II) and ESWT application (group III) on patients with OA and popliteal cyamella (Chen et al., 2014). The control group (group IV) maintained unchanged ROM of knees and weak muscle power all the time. While compared with group IV, group I-III showed significant differences in ROM as well as mean peak torque of knee flexion and extension in concentric and eccentric contraction at both 60°/second and 180°/second, and group III had the most excellent enhancement among the three modalities. The authors supported ESWT as an effective and useful disease-modifying treatment in the management of OA patients with popliteal cyamella (Chen et al., 2014). Interestingly, since the cyamella as a sesamoid bone is reported to occur in 10–30% population (Tabira et al., 2013), sesamoid syndrome takes place in a limited proportion of these individuals with OA. Therefore, can ESWT decrease the calcified areas of popliteal cyamella to have a better clinical improvement? Can the improvement in functional status prolong for the follow-up periods? Can these therapeutic effects extend and benefit all the OA patients? The answers are unknown and further studies are required.

4. Discussion

Shock waves initially adopted as standard therapy for kidney stones in lithotripsy. Later, effects on musculoskeletal system close to renal regions were detected. Shock waves have been introduced to treat various disorders such as tendinopathies, pseudarthrosis and nonunion or delay-union of bone.

On the basis of mechanotransduction theories, shock waves exert stress on cells from membrane to the nucleus via cytoskeleton and integrated mechanosensory system and finally lead to a broad range of biological effects, such as cell structure rearrangement, gene expression regulations and metabolic alterations through various signal pathways. What's more, ESWT enhances expression of the genes encoding TGF-β, insulin-like growth factor (IGF), and fibroblast growth factor (FGF), VEGFs, and BMPs, which are all crucial factors for cell growth, tissue repair, chondrogenesis and osteogenesis (Frairia and Berta, 2011). These therapeutic effects open up new horizons for the use of ESWT. One of the potential new applications is osteoarthritis. Researchers have made attempts to employ ESWT to treat OA and their efforts are not in vain. Intriguingly, ESWT showed chondroprotective and subchondral bone remodeling effects proved by histomorphological examinations and immunohistological analysis in a growing number of investigations. Moreover, emerging evidence has showed pain reduction and motor function improvements after shock waves stimulation. Although the favorable results are exciting, the exact mechanism of action causing these therapeutic effects by ESWT remains unknown. Regulating the expression of various kinds of cytokines such as IL-1, IL-10 and TNF-alpha to modulate the production of ECM, MMPs, BMP-2, osteocalcin via signal pathways, may be a part of the whole splendid picture to illustrate its benefits. ESWT may interfere with the pathological changes via intricate modulation of intra- and extracellular substances and ultimately present the improved clinical symptoms of OA.

In addition, little information has been published to discuss the treatment protocol of ESWT towards OA. Energy intensity, duration, treatment intervals and treatment numbers are not determined yet. Parameters such as frequency, energy flux density and impulses are often randomly combined together and vary from one study to another, which makes it difficult to analyze and compare the results in these investigations. Besides, responses to shock waves change with the use of different ESWT machines, intervention techniques and individual sensitivities. Increasing investigations are encouraged to establish the therapeutic regimen of ESWT in OA.

Last but not least, most OA patients especially the elderly suffer from bone fragility and more fall risks. Negative effects and application safety must be discussed here. Firstly, for chondrocytes, ESWT with an EFD more than 0.06 mJ/mm^2 had cytotoxicity and cell proliferation inhibition effects (Dorotka et al., 2003). Decreased chondrocyte viability and increased membrane permeability leading to apoptosis were also observed when too many impulses (4000) of shock waves applied (Byron et al., 2005). Interestingly, a recent study on human chondrocytes revealed that the survival of cells largely affected by their physical surroundings (Renz and Rupp, 2009). Numbers of dead cells significantly increased in fluid suspension shortly after the ESWT with 0.26 mJ/mm^2, while no cytotoxic effects were showed on chondrocytes in alginate. Alginate, a medium more viscous than liquid suspension, is very similar to the characteristic of viscoelastic cartilage in vivo to reduce the cavitation effects induced by shock waves. Therefore, the authors concluded that side effects of ESWT which are reported in several studies that used chondrocytes in liquid are less likely to occur in vivo. Chondrocytes deaths may not be expected in a clinical setting (Renz and Rupp, 2009). Secondly, as to joint cartilage of animal model, 2000 shock waves of 1.2 mJ/mm^2 caused no destruction to the femoral condyle of rabbits (Väterlein et al., 2000). Although rough-surfaced endoplasmatic reticulum expansion and cell membrane detachment were observed on the ultrastructural level after a single session of ESWT (EFD: 0.5 mJ/mm^2; Pulses: 1500), few pathological changes were found on hyaline cartilage of adult rats according to the criteria of Mankin (Mayer-Wagner et al., 2010). Finally, human patients received ESWT (Pulses: 2000; EFD: 0.03–0.4 mJ/mm^2) showed a high compliance of more than 90% in the clinical trial (Chen et al., 2014). And no specific side effects such as intolerable pain, tissue erosion or local swelling were reported. In addition, another randomized controlled trial proved the safety of shock waves. 4000 pulses ESW at 0.25 mJ/mm^2 and a frequency of 6 Hz showed significant effectiveness in pain relief and functional performance instead of the adverse events (Zhao et al., 2013). In all, ESWT may be a relative safe intervention not to cause more degenerative effects on osteoarthritis. However, more cautions are needed when adopting extremely high-energy shock waves.

5. Conclusion

Extracorporeal shockwave therapy is a novel and noninvasive physical therapy and appears to be a potential modality in the treatment of bone and cartilage disorders; for instance, osteoarthritis. Conclusive statements could be made until additional studies, especially clinical trials, to determine the long-term outcomes of effects and to validate the most appropriate treatment protocol of ESWT. Further studies into its mechanisms of action and applications in other musculoskeletal or osteochondral diseases are imperative for multidisciplinary partnerships.

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No.

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