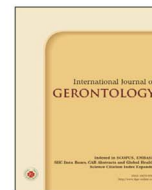




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Review Article

Extracorporeal Shock Wave Therapy in the Treatment of Knee Osteoarthritis: A Review of Mechanism of Action and Clinical Efficacy

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SUMMARY

Knee osteoarthritis (KOA) is the most common form of arthritis and one of the leading causes of disability. OA is characterized by cartilage damage, subchondral bone changes, and synovial tissue inflammation, with clinical symptoms of pain, decreased range of motion (ROM) and functional impairment. Recently, extracorporeal shockwave therapy (ESWT) has been introduced in the treatment of OA and there is increasing evidence of the therapeutic effects of ESWT on patients with KOA. For decades, there have been multiple attempts to understand the mechanisms of these therapeutic effects. So far, it is appreciated that cellular mechanotransduction through the cytoskeleton into the nuclei can regulate gene expression and cause biological changes. The purpose of this article is to provide current evidence on the physical and biological principles, mechanism of action and clinical efficacy of ESWT on KOA.

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1. Introduction

Osteoarthritis (OA) is a joint disorder characterized by structural pathology that involves the whole joint, including cartilage lesions, bone remodeling, osteophyte formation, and joint inflammation.¹ OA is the most prevalent chronic rheumatic disease and is a leading cause of pain and disability in most countries worldwide, with knee joints being the most commonly involved.² OA is a chronic condition, leading to a loss of joint cartilage, persistent pain and loss of function. The Global Burden of Disease Study 2010 indicated that knee OA (KOA) is the fastest increasing major health disorder and the second largest global cause of disability.³

With the acceleration of population aging, the morbidity of KOA is increasing. Previous studies reported that the lifetime risk of developing symptomatic KOA is around 45%.⁴ An increase in the prevalence of symptomatic KOA over the past 20 years has been noted in the Framingham cohort, rising by 4.1% in women and 6% in men.⁵ Based on National Health Interview Survey (NHIS) data, the estimated number of US adults with OA is projected to increase to nearly 67 million by 2030.⁶

Treatment for KOA focuses on alleviating pain, decreasing inflammation, restoring function and decelerating progression of the disease. According to Osteoarthritis Research Society International guidelines,⁷ initial management of KOA is conservative and consists of both non-pharmacological and pharmacological treatment, including weight loss (e.g., diet, nutrition), assistive devices (e.g., braces, canes), physical therapy, low-impact exercise (for activity modification), non-steroidal anti-inflammatory drugs, analgesic

drugs, as well as intra-articular injections (corticosteroid and hyaluronic acid),¹ but these may have limited efficacy. Total knee replacement often provides greater pain relief and long-term benefits, but is associated with a higher risk of adverse events,⁸ and many patients continue to have pain and disability despite surgery. In addition, total knee replacement might not be appropriate due to the patient's medical condition, or be limited by the availability and cost of the procedure. Because neither conservative nor surgical management of KOA guarantees success, an unmet need exists for novel therapies to provide pain relief and improve function. One of these therapies is extracorporeal shockwave therapy (ESWT).

ESWT was initially introduced to disintegrate renal stones in the 1980s. Since then, there has been growing knowledge of its biological and therapeutic properties. In the recent 20 years, studies have shown evidence that ESWT can treat various musculoskeletal,⁹ neurological,^{10,11} and inflammatory tendon diseases.¹² Recently, ESWT has been introduced in the treatment of OA, including KOA. This review will give an overview of ESWT in treating KOA with regards to its potential mechanism of action and clinical therapeutic effects.

2. Physical principles and generation of shock wave

2.1. Pressure waves

ESWT is a pressure wave applied externally to the body, leading to energy transmission within and absorption by body tissues. A shockwave is a non-linear type of sound wave, characterized by high peak-pressure amplitudes (500 bar) with short rise time and short duration (10 ms). After reaching the positive peak, the pressure drops to negative values within microseconds. During the positive

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phase, shockwaves produce direct mechanical forces and hit interfaces, leading to refractions, or pass through and gradually are absorbed. The negative phase of the shockwave causes cavitation and gas bubbles that subsequently implode at high speeds, generating a second shockwave.¹³ These events cause direct (physical) and indirect (biological) effects on the treated tissue.¹³ There are several primary parameters utilized to describe shockwaves. Energy flux density (EFD), 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),¹⁴ can be classified as high-energy ($\text{EFD} > 0.12 \text{ mJ}/\text{mm}^2$) and low-energy ($\text{EFD} \leq 0.12 \text{ mJ}/\text{mm}^2$).¹⁵ Pressure (bar/kV/Pa) or energy levels (low/high) are also used to determine the energy density of shockwaves. The total amount of energy delivered per session is determined by multiplying the EFD by the number of shockwaves delivered.

3. Types of ESWT

Focused shockwave therapy and radial shockwave therapy are two types of shockwave therapy used in clinical practice.¹⁶ These shockwaves differ in method of production, physical characteristics, and energy delivered (Table 1).

Focused shockwaves are generated by electrohydraulic, electromagnetic, and piezoelectric devices. Radial shockwaves are typically produced by pneumatic/ballistic devices. Radial shockwaves show a lower peak pressure, relatively low velocity of propagation, and a longer rise time than focused shockwaves. Focused shockwaves carry more energy than radial shockwaves. Focused shockwaves generate maximal force at a selected depth, affecting a small, precisely defined area; radial shockwaves generate highest pressure at the skin surface with subsequent weakening at greater depth, affecting a larger, more diffuse area. Based on the strength of current evidence, the International Society for Medical Shockwave Treatment has developed a list of approved clinical indications of focused and radial ESWT on the musculoskeletal conditions (Table 1).¹⁷

3.1. Mechanical effect and biological response of ESWT

Despite the clinical effectiveness of ESWT, its mechanism of action remains unclear. It has been proposed that ESWT produces physiological effects by direct (mechanical) and indirect (chemical/biological) mechanisms. Positive pressure and the consequent negative pressure are the typical features of a shockwave, which cause different effects on the target tissue. A shockwave firstly evokes compression during the positive phase, then shear stress from the negative phase may exert cavitation effects on a focal area. These complex mechanical forces together exert pressure on extracellular matrices to cause deformation of cell structures and alter cellular

cytoskeleton by stimulating sensory units in the cell membrane. The forces also activate ion channels in the cell and change signaling pathways, which may lead to alterations in gene expression and cellular behavior.¹⁸ These effects include enhanced neovascularity, accelerated growth factor release, selective neural inhibition, osteogenic stem cell recruitment, and inhibition of molecules that have a role in inflammation.

3.2. Potential mechanism of ESWT on KOA

The exact mechanism of action of ESWT in KOA is still unknown. However, there are several biomechanical and physiological activities that may partially explain its clinical benefit. It has been hypothesized that mechanotransduction of the shockwave impulse induces biological effects on cartilage, subchondral bone and pain sensation, resulting in clinical effect (Figure 1).

3.3. ESWT on articular cartilage

Articular cartilage deterioration is one of the main features observed in patients with OA. Loss of the cartilage cushion causes friction between the bones, leading to pain and limitation of joint mobility. Therefore, a favorable turn of cartilage function aimed at improving arthritic symptoms must be involved in the management of OA. Many investigations demonstrated that ESWT might have chondroprotective and chondrogenesis effects.¹⁹ C-telopeptide of type II collagen (CTX-II) and matrix metalloproteinase (MMP) are common markers of cartilage damage. In a rat KOA model, application of ESWT resulted in the decrease of CTX-II concentration and MMP expression. Studies on chondrocytes *in vivo* have shown that ESWT may decrease the production of tumor necrosis factor- α (TNF- α).²⁰ TNF- α mediates a wide range of biochemical reactions, including activation of MMP synthesis and chondrocyte apoptosis.²¹ Therefore, the decreased level of TNF- α may partially explain the chondroprotective mechanisms of ESWT.²⁰ Some studies demonstrated potential benefits of decreased production of nitrous oxide by ESWT.²² Nitrous oxide mediates the inflammatory response and is associated with the expression of MMPs. Therefore, a decreased level of nitrous oxide may result in a reduced catabolic rate of articular cartilage. As these factors modulate cartilage homeostasis, they are postulated to be involved in the initiation and progression of OA. Together, these actions may partially elucidate the mechanisms of ESWT on chondroprotective effects and cartilage repair. In a rabbit OA model, ESWT ($0.12 \text{ mJ}/\text{mm}^2$, 500 pulses at 1 Hz) improved chondrocyte distribution and viability, and inhibited abnormal location of cartilage mineralization. The results are similar to Lyon et al.'s study, which showed shockwaves enhanced cartilage healing rate and facilitated hyaline-like cartilage production.²³

Table 1

Waveform characteristics of focused and radial ESWT.

	Focused ESWT	Radial ESWT
Pressure	10–100 MPa	0.1–1 MPa
Energy	About $1.5 \text{ mJ}/\text{mm}^2$	$< 0.3 \text{ mJ}/\text{mm}^2$
Pulse time	< 10 microseconds	> 1 milliseconds
Penetration depth	Deep	Superficial
Wave propagation	Concentration due to focusing	Reduction of energy due to propagation attenuation
Percutaneous speed of entry	Approximately 1500 M/second	Approximately 2–20 M/second
Therapeutic effect zone	Main effect at deep focused zone	Main effect at superficial distracted zone
Clinical indications	Lateral epicondylitis of the elbow, Patellar tendinitis, Plantar fasciitis	Calcifying tendinopathy of the shoulder, Lateral epicondylitis of the elbow, Patellar tendinitis, Plantar fasciitis, Delayed bone healing, Bone non-union, Stress fracture, Avascular bone necrosis

Abbreviation: ESWT, extracorporeal shockwave therapy.

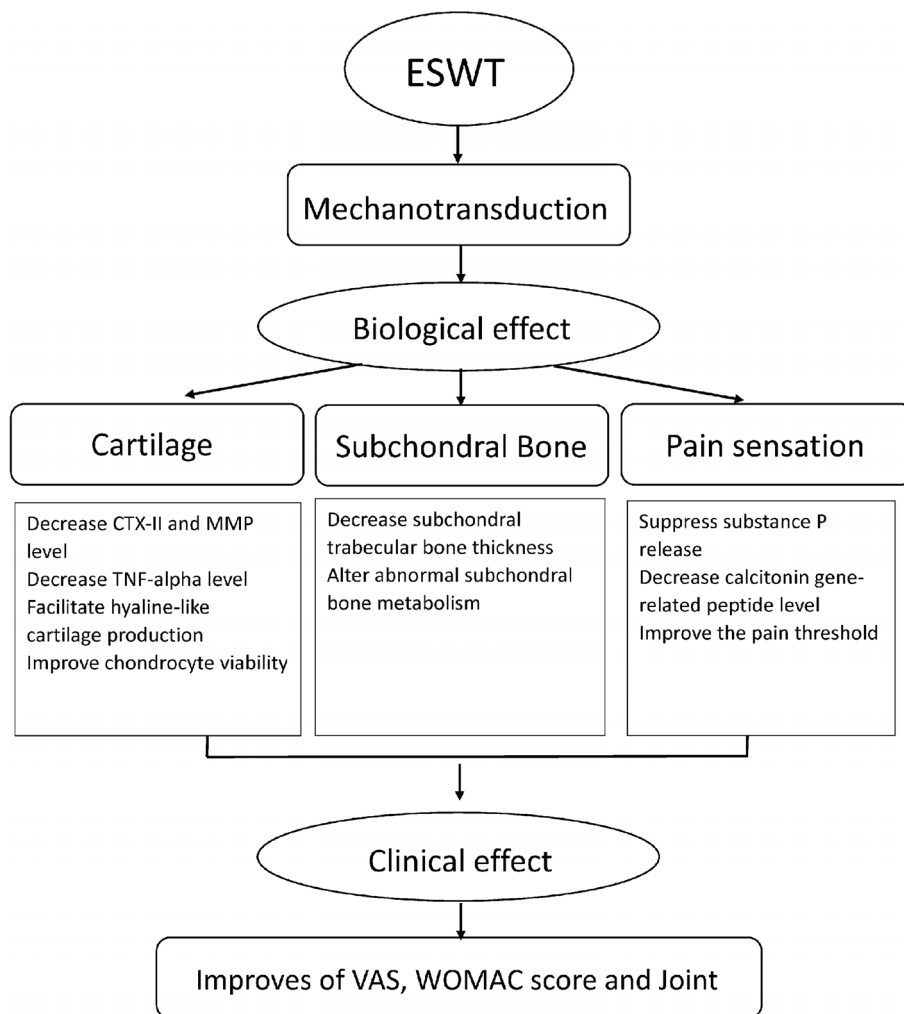


Figure 1. The potential mechanism of action for ESWT in knee OA. Abbreviation: ESWT, extracorporeal shockwave therapy; OA, osteoarthritis; CTX-II, C-telopeptide of type II collagen; MMP, matrix metalloproteinase; TNF-alpha, tumor necrosis factor-alpha; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ROM, range of motion.

3.4. ESWT on subchondral bone

Subchondral bone sclerosis, together with progressive cartilage degradation, is widely considered a hallmark of OA. The pathognomonic signs of OA on plain radiographs are joint space narrowing, osteophytes, subchondral sclerosis and subchondral cysts. Increased subchondral bone stiffness and sclerosis may decrease the ability of the knee joint to distribute the mechanical force load on the overlying articular cartilage. Consequently, the increased abnormal force load on the cartilage might accelerate damage and degeneration.²⁴ In a rat anterior cruciate ligament transection model of KOA, significantly higher percentage of subchondral trabecular bone and increased numbers of osteocytes were detected in the ESWT-treated group compared to untreated groups.²⁵ An additional study showed that ESWT may result in better tissue distribution of cortical bone, cancellous bone and fibrous tissue.¹⁹ These findings concur with that of Wang et al., who found ESWT resulted in decreased subchondral trabecular bone thickness, mineral density and bone volume.²⁵ Taken together, this suggests ESWT alters abnormal subchondral bone metabolism and protects against abnormal subchondral bone remodeling.

3.5. ESWT on pain sensation

The most common symptom of KOA is pain around the knee

joint. Pain can be dull, sharp, constant, or intermittent. Gradual joint swelling, stiffness, deformity and functional limitations may aggravate symptoms. Despite treatment, most patients continue to experience pain. Therefore, alleviation of pain should be an important part of managing KOA. The exact mechanisms of ESWT mediating pain relief in KOA are still unknown. Substance P and calcitonin gene-related peptide (CGRP) are important neuropeptides in nociceptive processes and contribute to the nociceptive input from joints in different types of spinal cord neurons.²⁶ Augmented production of CGRP in the dorsal root ganglia increases the pathological response in the chronic inflammatory knee joint. In a rat model of KOA, ESWT was shown to reduce the number of neurons immune-positive for calcitonin gene-related peptide when compared to control animals. This is in concordance with the results of Hausdorf et al., who found that application of ESWT to the distal femur of rabbits diminished the number of substance P-immunoreactive neurons in the dorsal root ganglia of L5.^{27,28} The authors suggested that shockwaves inhibit nerve fibers from transmitting pain information by degenerating nerve endings and helping to reduce the number of CGRP-immunoreactive DRG neurons, ultimately leading to pain relief.²⁷ Some studies suggest that ESWT may relieve pain by suppressing substance P release.²⁹ Additionally, ESWT can act directly on peripheral sensory nerve endings, improving the pain threshold and propagation of the pain signal.²⁹

3.6. Clinical evidence of ESWT on knee OA

Zhao et al.³⁰ performed the first randomized controlled trial (RCT) of ESWT in 70 patients with KOA. In the ESWT group, patients received 4000 pulses of shockwave at 0.25 mJ/mm² weekly for four weeks. In the placebo group, patients received shockwave at 0 mJ/mm² in the same area. Patients treated with ESWT exhibited significant improvements in pain score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and the Lequesne index. The authors concluded that ESWT was effective at reducing pain and improving knee function. This was concur with subsequent RCTs,^{31–35} which also showed ESWT had a beneficial effect on pain relief and physical function improvement in patients with KOA. However, Imamura et al.³⁶ randomized 105 patients with moderate or severe KOA to either radial ESWT (3 sessions, 2,000 radial ESWT impulses per session, energy flux density 0.10–0.16 mJ/mm²) or placebo. The results showed radial ESWT led to a statistically significant improvement only in mean WOMAC scores for pain, but not in stiffness or physical function score. Recently, Wang et al. conducted a systematic review of 9 studies that assessed the efficacy and safety of ESWT for KOA.³⁷ The authors concluded that ESWT has a beneficial effect on pain relief and physical function for up to 12 months, with only minor complications after treatment. A retrospective study investigated the efficacy and safety of ESWT combined with hyaluronic acid for patients with KOA. The results showed that patients in the combined ESWT and hyaluronic acid group exhibited better efficacy in visual analog scale (VAS) and WOMAC scale, with no significant differences regarding adverse events between the two groups.³⁸

ESWT has also been compared to other treatment methods. Elerian et al. published a prospective randomized controlled study involving 73 patients with KOA who received either corticosteroid injection, ESWT treatment or sham shockwave treatment. Patients in the injection group received 40 mg of methylprednisolone with 2 mL of 2% lidocaine. Those in the ESWT group received three sessions of 2,000 shockwaves at a pressure of 2 MPa. Patients in the control group received sham shockwave treatment. Significant improvement of VAS score and ROM was seen in both the shockwave group and corticosteroid injection group compared to the sham group, and greater improvement was seen in the ESWT group than corticosteroid injection group for VAS score, ROM and WOMAC score. An RCT by Lee et al. on 61 patients with KOA compared the effects of ESWT and intra-articular injections of hyaluronic acid. The authors found improvement in both groups, with no significant difference between the two groups.³⁹ A systematic review and meta-analysis by Li et al. to evaluate the efficacy and safety of ESWT for treatment of KOA also found that ESWT may achieve a better therapeutic effect for patients with KOA compared to physical therapy and placebo.⁴⁰

Dose-related effects of ESWT for treatment of KOA have been observed. 60 patients with KOA were randomized to high-energy treatment group (energy flux density, 0.093 mJ/mm²) or low-energy treatment group (energy flux density, 0.040 mJ/mm²). After treatment, both groups showed significant improvement in pain relief and functional outcomes over time, and the high-energy group showed greater improvement.⁴¹

Based on the above findings, ESWT might be a novel and effective treatment method for KOA. Although the exact mechanism of action of ESWT in KOA in humans is not fully understood, ESWT might exert stress on cells from the membrane to the nucleus via the cytoskeleton and integrated mechanosensory system. After sensing and processing mechanical information from the extracellular environment, these mechanical forces are converted into biochemical

responses, thus leading to a broad range of biological effects, such as cell structure rearrangement, gene expression regulations and metabolic alterations. Most histological and immunochemistry studies demonstrate that ESWT show chondroprotection, subchondral bone remodeling and pain reduction. These findings may help explain the clinical effects of ESWT on KOA. However, there are still many unanswered questions. Few studies have investigated the treatment protocol of ESWT for KOA. The optimal dosage, treatment duration, treatment intervals and treatment sessions have not yet been determined. Parameters such as frequency, energy flux density and impulses and types of ESWT also remain to be explored.

4. Conclusions

Given the prevalence of knee OA, which is projected to increase substantially in aging populations, there is a clear need for novel effective conservative therapies to improve patient symptoms and function. ESWT, in virtue of its noninvasiveness, absence of major side effects, reproducibility, tolerability, and good compliance by patients, seems to offer a new therapeutic modality for patients with KOA. Available animal and clinical studies show that ESWT is an effective, novel and noninvasive method to reduce pain and improve physical function in patients with KOA. Further studies delving into its exact mechanisms of action and optimal treatment protocol and parameters are imperative to help make an evidence-based decision when managing KOA.

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