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Extracorporeal Shockwave Therapy for the Treatment of Tendinopathies: Current Evidence on Effectiveness, Mechanisms, Limitations, and Future Directions

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ABSTRACT

Tendinopathy is a chronic degenerative tendon disorder which is characterised by pain, swelling and impaired physical function and performance, presenting in both athletes and the general population. Extracorporeal shockwave therapy (ESWT) is an increasingly common treatment for tendinopathy, which can initiate tendon healing and regeneration. The review presents current understanding of mechanisms of action of ESWT and provides a brief overview of its history and development. The central purpose of the review is to synthesise research findings investigating the effectiveness of ESWT for seven common tendinopathies (plantar

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heel pain, rotator cuff, lateral elbow, Achilles, gluteal, hamstring and patellar tendinopathy) and provide recommendations on clinical applicability. Collectively, the available evidence indicates that ESWT is effective and can be recommended in treatment for the seven tendinopathies. However, the evidence is stronger for certain tendinopathies compared to others and uncertainties remain regarding the optimal ESWT treatment parameters. The consensus from recent literature is that although ESWT can be effective in isolation it should be combined with other treatments in tendinopathy, which needs to be addressed in future research.

Keywords: High-Energy Shock Waves; Tendinopathy; Resistance Training; Extracorporeal Shockwave Therapy; Musculoskeletal Diseases

1. Introduction

The recent global burden of disease study highlighted that musculoskeletal disorders are a leading cause of global disability and morbidity [1]. Tendinopathy is one of the most prevalent musculoskeletal disorders, responsible for 30-50% of all sports injuries [2]. Tendinopathy is a degenerative tendon disorder which is characterised by chronic pain, diffuse or localised swelling and impaired physical function and performance [3]. Tendons are susceptible to injury as they undergo high forces during repetitive sports activities, receive little vascular blood supply, have low elasticity and decreased metabolism compared to other tissues [4]. Histopathological findings in tendinopathy include collagen disorganisation and fibre separation, hypercellularity, increased mucoid ground substance and neovascularisation, without signs of inflammation [5]. However, the noninflammatory aetiology of tendinopathy has been challenged as inflammation is considered to play a key role in the initial phases of the disorder [6]. Recent European studies on lower limb tendinopathies estimate incidence and prevalence ranging from 7.0-11.8 and 10.5-16.6 per 1000 people, respectively [7, 8]. The aetiology and pathogenesis of tendinopathy is considered multifactorial, resulting from a range of extrinsic and intrinsic factors [9]. Identified risk factors include impaired biomechanics [10], rheumatological and metabolic disorders [11], excess adiposity [12] fluoroquinolones [13]; genetics [14], and central nervous system hypersensitivity [15].

A range of approaches are used in tendinopathy rehabilitation including anti-inflammatory medications, corticosteroid injections, laser therapy, ultrasound, platelet-rich plasma injections, prolotherapy, glycerol trinitrate patches, manual therapy, and various types of exercise [16]. Extracorporeal shockwave therapy (ESWT) is an emerging treatment option with a growing body of research investigating its applicability and effectiveness as a tendinopathy treatment [17, 18]. Due to its non-invasive nature, dearth of side effects, short duration and patient acceptability, ESWT offers a therapeutic rehabilitation method, when other conservative treatments are ineffective [19]. The purpose of this review is to synthesize the current available research on effectiveness of ESWT for seven tendinopathies (plantar heel pain, rotator cuff, lateral elbow, patellar, gluteal, hamstring and Achilles). The review will begin with an overview of the history of ESWT and its physical mechanisms, progressing to mechanisms of action for ESWT. Following an overview of the evidence on effectiveness of ESWT for tendinopathies, the review will conclude with considerations of the limitations of treatment parameters, future research needs and clinical recommendations.

2. Methodology

To conduct this narrative review, a systematic literature search was conducted using Medline/PubMed database to identify studies up to May 2020 using a combination of the following search terms: extracorporeal shockwave therapy, shock wave, shockwave therapy, shockwave, ESWT, tendon, tendinopathy, musculoskeletal, plantar, Achilles, patellar, rotator cuff, elbow, epicondylitis, gluteal, and hamstring. Relevant articles were retrieved and used to identify additional sources by cross-referencing and manually checking reference lists.

3. ESWT history and development

The effects of shockwaves on humans were first discovered during the Second World War, when German scientists discovered that shockwaves from a distant explosion could damage lung tissue [20]. In 1971 the first non-direct kidney stone disintegration was reported, leading to the development of the first clinical shockwave machines and human research [21]. The use of shockwaves in medicine began in Germany in 1980 with extracorporeal shockwave lithotripsy as a treatment to disintegrate renal and ureteric calculi [22]. In urological research, the discovery of new bone formation on pelvic bones was incidentally observed adjacent to the path of delivered shockwaves [23]. Consequently, further research identified the potential for both destructive and regenerative effects of shockwaves in human tissues [24]. Experimental research elucidated a dose-dependent response, with high-energy shockwaves being destructive and low-energy shockwaves causing regeneration in tissues [25]. Investigations into fracture healing concluded that better outcomes are achieved in treating bone non-unions, with ESWT successfully used as a treatment for non-union fractures in 1988 [26]. From the early 1990s the beneficial effects of ESWT on musculoskeletal disorders began emerging, leading to the development of focused ESWT (F-ESWT) devices, designed specifically to treat musculoskeletal disorders [27]. The destructive potential of high-energy ESWT was first applied to rotator cuff tendinopathies of the shoulder with extraosseous calcification, allowing for calcific deposit disintegration [28]. Next, low-energy F-ESWT was tested with other chronic tendinopathies, beginning with plantar fasciopathy and then lateral elbow tendinopathy, showing beneficial regenerative effects [29]. In the early 2000s new devices with ballistic pressure waves were introduced, referred to as radial ESWT (R-ESWT), with clinical effectiveness found for superficial musculoskeletal disorders [30]. Today ESWT is a widely accepted clinical treatment, which is applied to a broad range of musculoskeletal disorders and is considered a significant innovation in regenerative medicine [31].

4. Physical mechanisms of shockwaves

Shockwaves can be defined as mechanical acoustic energy waves, with positive pressure followed by negative pressure, and returning to ambient values within microseconds [32]. Shockwaves are sonic pulses characterised by high peak pressure amplitudes of up to 100mpa (500 bar), with rapid pressure rise times under 10 nanoseconds, a short lifespan of under 10 microseconds and a broad frequency range, usually 16-20 MHz [33]. Because of the rapid pressure increases, shockwaves have been compared to 'micro explosions' [33]. High pressure shockwaves produced in the positive phase can be reflected or absorbed, whereas the negative phase causes formation of cavitation bubbles due to negative pressure at tissue interfaces [34]. Cavitation bubbles implode at high speed, generating subsequent shockwaves or fluid microjets, which stimulate direct and indirect effects on tissues [35]. The peak pressure generated by shockwaves are typically 1000 times greater than that created by therapeutic ultrasound [19]. Focused shockwaves are typically generated through a fluid medium, by either an electrohydraulic, piezoelectric, or electromagnetic type source generator [32]. Electro-pneumatically generated radial shockwaves do not technically form shockwaves, rather radial pressure waves, which can induce acoustic cavitation via a ballistic mechanism [36]. Compressed air accelerates a projectile, typically a bullet inside a cylindrical handpiece. When the projectile hits an applicator at the end of the tube, high-energy pressure waves are produced which radially expand from the skin into tissue in spherical waves [34]. Unlike F-ESWT, the waves are not focused into small deeper tissues, therefore are suitable for treating large superficial tissues [36]. Despite these differences, each generator type focuses pressure impulses into the targeted tissue which mechanically stimulate cells through mechano-transduction, activating biochemical signalling and tissue regeneration [37].

5. General mechanisms of action

Despite evidence indicating effectiveness of ESWT across a plethora of medical conditions, its mechanisms of action remain not fully understood. Haupt [25] proposed four possible phase mechanisms of ESWT effects on tissue: physical, physicochemical, chemical, and biological. In the physical phase, shockwave pressures cause absorption, reflection, refraction, and transmission of energy into cells. These tensile forces induce cavitation, increasing cell membrane permeability and activating cell signalling pathways [33]. These include mechano-transduction pathways and those that regulate a variety of gene expressions [38].

In the physicochemical phase cells release molecules such as adenosine triphosphate (ATP), activating cell signalling pathways [39]. In the chemical phase, ion channels in cell membranes are altered allowing cell calcium mobilization [40]. The biological phase plays host to a plethora of identified biological responses due to tissue and cell stimulation [41]. Tissue-healing responses are mediated by release of vascular endothelial growth factor (VEGF), endothelial progenitor cells, endothelial nitric oxide synthase (eNOS), insulin-like growth factor (IGF-1) proliferating cell nuclear antigen (PCNA) and various other functional proteins [31, 42]. Cellular modulation is activated by upregulation and downregulation of proteins which promotes processes such as neovascularization [43], anti-inflammation [44], anti-apoptosis [45], chondroprotective effects [46], angiogenesis [47], and regeneration of bone and tendon tissue [48]. Additionally, ESWT activates immune system responses [49] and anti-inflammation by stimulating macrophage, T-cell, and mesenchymal stem cell proliferation [50-52). ESWT also modulates expression of inflammatory cytokines such as interleukin-6, interleukin-10 and tumour necrosis factor alpha, leading to anti-inflammatory effects [53].

Another proposed mechanism of ESWT on mechanobiology is its influence on the nervous system and neurophysiological processes. Research has reported analgesic effects of ESWT, which may be due to modulating neurological responses, although exact mechanisms are unknown [54]. However, ESWT has been shown to modulate the presence or function of unmyelinated nerve fibres and pain neurotransmitters such as substance P [55] and calcitonin gene-related peptide [56]. Nociceptor hyperstimulation and stimulation of nociceptive C-fibres can also release pain inhibiting substances such as neuropeptides [57]. Studies have also shown the potential of ESWT in reducing hypertonia and spasticity and regenerative effects on nerves and spinal injuries [58, 59]. Wess [60] identified how ESWT could reorganise pathological memory pathways leading to permanent pain relief, due to the mitigation of pain central sensitization, which is believed to play a key role in chronic pain experienced in tendinopathy. Recently transcranial F-ESWT was found to increase vigilance in those with unresponsive wakefulness syndrome and improve symptoms in polyneuropathy [61]. Further research is required to determine the exact neurophysiological mechanisms exerted by ESWT and their full potential.

5.1 Tendon specific mechanisms of action

Chronic tendinopathies have historically had poor outcomes with traditional treatment methods, however ESWT may exert a plethora of direct healing effects on tendon tissue during treatment [62]. Treatment with ESWT can influence cell homeostasis and tissue regeneration by stimulating healing responses, such as inducing proliferation, differentiation, and migration of mesenchymal stem cells [63]. However, shockwaves can target many cell types, including stromal cells, endothelial cells, osteoblasts, fibroblasts and tendon specific tenocytes and collagen [31]. In vitro studies have also found shockwaves activate tendon repair processes by increasing normal fibroblast proliferation and activating gene expression for Transforming growth factor beta 1 and for collagen types I and III [64]. Several other tendon specific responses have been observed, including reduction in matrix metalloproteinases and inflammatory cytokines, and upregulation of tendon cells and anti-inflammatory cytokines [53]. There is also proliferation and migration of proteins involved in collagen synthesis and tenocytes in damaged tendons and increased lubricin expression, stimulating healing [65, 66]. The mechanical stimulus of ESWT has been postulated to generate tendinopathy collagen synthesis and remodelling by promoting catabolic and inflammatory processes and stimulating removal of pathological matrix constitutes [48]. The following sections will summarise the evidence of clinical effectiveness of ESWT for specific tendinopathies.

6. Clinical effectiveness of ESWT

6.1 Rotator cuff tendinopathy

Rotator cuff tendinopathy is thought to be caused by a combination of extrinsic and intrinsic mechanisms leading to chronic tendon degeneration, although its aetiology is not fully understood [9]. The disorder is characterised by persistent pain, disability and weakness in the shoulder, especially when lifting overhead or abducting the arm beyond 90 degrees [67]. Prevalence is estimated to be as high as 14% in the general population [68] and has been reported as high as 30% in volleyball players [69]. Rotator cuff tendinopathy can lead to long-term disability, with up to 42% reporting symptoms after ten years [70]. Calcific rotator cuff tendinopathy is thought to be caused by repetitive mechanical overloading leading to calcium hydroxyapatite deposition, with 80% of cases involving the supraspinatus tendon [71]. Although eccentric exercise can be effective [72], ESWT has emerged as an alternative treatment option prior to surgery [73] and has been found equally effective as supervised exercise [74]. Several systematic reviews and meta-analysis have been published on ESWT and rotator cuff tendinopathy, with similar positive findings [75-85].

Huisstede et al. [75] concluded that only high-energy ESWT is effective for calcific rotator cuff tendinopathy, with no evidence for non-calcific rotator cuff tendinopathy. Similarly, Bannuru et al. [76] concluded high-energy ESWT is effective for improving function and pain in calcific rotator cuff tendinopathy and can result in complete calcification resolution, unlike low-energy ESWT or placebo. A meta-analysis by Verstraelen et al [77] also found high-energy ESWT better at improving function and calcific reabsorption compared to low-energy ESWT. A recent comprehensive systematic review and network meta-analysis comparing all non-surgical treatment for calcific rotator cuff tendinopathy included 14 RCTs and concluded that F-ESWT is the best treatment for improving pain, function and calcium deposit resolution [78]. Several other reviews also concluded that ESWT is safe and effective in calcific rotator cuff tendinopathy, with ESWT improving shoulder function, reducing pain and calcific deposits, with efficacy maintained at 6-month follow-up [79-81]. Several high quality randomized controlled trials (RCTs) as assessed by these reviews have found significant benefit of ESWT in calcific rotator cuff tendinopathy [28, 82-84]. Despite compelling evidence and recommendations for calcific rotator cuff tendinopathy, none of these reviews or others recommend ESWT for non-calcific rotator cuff tendinopathy [85]. Several RCTs have not found any benefit, therefore its use can be controversial and often not recommended [86, 87]. However, many of these studies fail to clarify the exact clinical diagnosis in patients and satisfactory results have been found in RCTs with strict inclusion criteria and clinical diagnosis for non-calcific rotator cuff tendinopathy [88].

6.2 Lateral elbow tendinopathy

Lateral elbow tendinopathy is caused by repetitive microtrauma of the extensor carpi radialis brevis muscle and tendon leading to chronic degeneration [89]. The disorder has been previously referred to as 'tennis elbow' or 'Lateral epicondylitis', suggesting an inflammatory disorder [90]. Symptoms include lateral elbow pain which can radiate down the arm and weak grip strength [91]. Recreational sports, increased age, smoking, diabetes, repetitive work tasks using the hands or wrists are risk factors, with prevalence as high as 2.8% in the general population [92] and up to 13.1% in climbing athletes [93]. Eccentric exercise has shown good outcomes for improving pain and function and is recommended as first-line conservative treatment [94]. However, exercise applied in isolation is considered to have low long-term effectiveness, suggesting other more effective treatments are warranted [95]. Although ESWT has been shown to be an efficacious treatment for lateral elbow tendinopathy, it is not without controversy as some RCTs have provided conflicting results [96-100].

A systematic review of nine RCTs by Buchbinder et al. [101] concluded there was high level evidence that ESWT provides little or no benefit for pain and function in lateral elbow tendinopathy. A systematic review by Rompe and Maffulli [102] including ten RCTs also acknowledged conflicting results, although the authors identified significant methodological heterogeneity and flaws throughout the studies. Only five RCTs had high quality placebo-controlled methodology, two of which reported significant success of ESWT over placebo [103, 104]. Three other high-quality trials not finding benefit still had important quality deviations in their study design from the previous two [105-107]. Three lower quality treatment-controlled trials reported effectiveness of ESWT [108-112]. Despite methodological heterogeneity, the authors concluded there was effectiveness of

ESWT for lateral elbow tendinopathy when well-defined restrictive study parameters are appropriately implemented. A recent systematic review and meta-analysis included 13 studies and 1035 patients comparing ESWT with other treatments for lateral elbow tendinopathy [113]. Meta-analysis showed that ESWT was superior for pain and function (loss of grip strength) compared to other treatment methods. Another recent meta-analysis including 12 studies concluded that R-ESWT was superior to F-ESWT for pain and function (grip strength) but only at short-term follow-up of 24-weeks [114]. Similarly, a meta-analysis including 5 RCTs comparing ESWT with ultrasound, found superiority of ESWT for pain and grip strength improvement at one, three and six months [115]. Another meta-analysis including 4 studies comparing ESWT with corticosteroid injections, found ESWT superior for pain and grip strength at 12 weeks [116].

6.3 Patellar tendinopathy

Patellar tendinopathy or 'jumpers' knee' results from repetitive microtrauma to the patella tendon causing an initial inflammatory response progressing to chronic degeneration [4]. Prevalence in the general population is around 14% [117], and as high as 30-45% in elite jumping athletes such as basketball and volleyball players, due to repetitive jumping and excessive knee loading [118]. Despite being challenging to treat, eccentric loading exercise such as decline squats can be useful for management of the disorder [119]. However, ESWT has been found more effective than stretching and strengthening exercises for the quadriceps and hamstrings [120]. Mani-Babu et al. [17] conducted a systematic review including seven studies on ESWT for patellar tendinopathy [120-126]. It concluded that ESWT is a promising short and long-term treatment for patellar tendinopathy, although the evidence is limited and further RCTs with robust design are needed. A systematic review by Korakakis et al. [18] concluded there was moderate-level evidence that ESWT is no more effective than placebo in short and mid-term for patellar tendinopathy. The authors also concluded there was low level evidence that ESWT is superior to standard conservative treatment in long-term outcomes. The review included 5 studies [120, 124, 127-129], with three [120, 124, 129] having significant methodological flaws, and the other two did not compare ESWT with placebo control [127, 128]. Despite claiming to use robust methods and quality assessment tools, high quality ESWT studies were not included, which may explain the inconsistent results. The authors acknowledged the need for methodological standardisation, suitability of quality assessment tools and reporting guidelines in future ESWT study design [18].

Despite ESWT having generally positive outcomes for patellar tendinopathy, studies have used extremely variable treatment parameters, leading to controversies regarding treatment protocols, effectiveness and recommendations [130]. There have been conflicting findings in RCTs investigating ESWT for patellar tendinopathy, with some finding no significant differences [124, 127, 129]. However, the studies reporting poor results have been rife with methodological flaws, questioning their reliability [131]. All the RCTs with robust methodological design have found positive effects of ESWT, quantifying the recommendations made by Mani-Babu et al. [17] and others [117] recommending its use for patellar tendinopathy. Two recent systematic reviews and meta-analysis comparing all treatments for patellar tendinopathy, both concluded that platelet-rich-plasma injections were the most superior treatment but did acknowledge that ESWT was effective for pain and function to a lesser extent [132, 133].

6.4 Achilles tendinopathy

Achilles tendinopathy is caused by repetitive microtrauma of the Achilles tendon and failed healing, leading to chronic degeneration, with evidence of inflammation being histologically absent [134]. Intrinsic and extrinsic risk factors include impaired biomechanics, overtraining, high body mass index, fluoroquinolone use, and history of metabolic or inflammatory disorders [135, 136]. Symptoms including pain, disability and tendon swelling typically last six months with up to 15% being symptomatic five years after diagnosis [137]. Achilles tendinopathy is common in athletes, particularly runners, with prevalence reported as high as 12.5% in adult athletes [138] and 7.8% in adolescent runners [139]. However up to 30% of cases present in those who do not participate in sports activities [140].

Heavy slow resistance training and eccentric exercise such as the 'Alfredson protocol' have shown good outcomes [141]. However, progressive eccentric exercise has been found less effective than ESWT alone for chronic insertional Achilles tendinopathy [142]. In unresponsive cases surgery may be required, however ESWT has emerged as a potential alternative treatment prior to surgery [143].

The systematic review by Mani-Babu et al. [17] included 11 studies on Achilles tendinopathy, four with midportion Achilles tendinopathy [144-147], two with insertional Achilles tendinopathy [142, 148], and five with both [149-153]. Despite some conflicting findings from studies comparing ESWT to sham [149], the results indicated overall that ESWT is an effective short-term intervention for pain and function in Achilles tendinopathy and should be recommended in clinical practice. There is also some low-quality evidence for long-term effectiveness [17]. Another systematic review concluded there was moderate evidence for F-ESWT in midportion and insertional Achilles tendinopathy [85]. The systematic review by Korakakis et al. [18] concluded there was low level evidence that ESWT is comparable to eccentric exercise and superior to no treatment for midportion Achilles tendinopathy and superior to eccentric exercise for insertional Achilles tendinopathy. Other systematic reviews have concluded that while ESWT is an effective treatment for pain and function, it may not be superior to eccentric exercise and may be more effective when combined with it [154-156]. Despite overall good evidence, all these reviews acknowledged that longer-term follow-ups from higher quality RCTs with strict study design are needed to build upon the evidence for Achilles tendinopathy.

6.5 Plantar heel pain

Plantar heel pain (PHP) is thought to be caused by repetitive microtrauma leading to degenerative shortening of the plantar fascia collagen matrix and possible heel spur formation [157]. The previously used diagnosis 'plantar fasciitis' suggested an inflammatory origin, and although inflammatory cells are present, chronic degeneration is considered the primary cause of the condition [158]. Moreover, the term 'plantar fasciopathy' is considered a more accurate diagnosis describing the chronic degenerative changes of the fascia, with many experts considering the condition to present like a tendinopathy [157]. Symptoms include heel pain in the morning and after activity or rest, and functional limitations such as impaired gait and reduced physical activity [159]. PHP has a lifetime prevalence of 10% in the general population [160], with prevalence ranging from 5.2% to 17.5% in running athletes [161]. A variety of treatment approaches have shown good short-term outcomes for PHP, including plantar-fascia specific stretching and resistance training either in isolation or combined with corticosteroid injections [162]. However, due to inadequate long-term outcomes of treatment, more effective treatments are required [163, 164]. Several systematic reviews and meta-analyses have concluded there is long-term safety and efficacy of ESWT, recommending its use for PHP [165-180].

A systematic review by Rompe et al. [165] included all 17 RCTs on F-ESWT for PHP published at that time, five of which were determined to be of good quality. They highlighted significant heterogeneity in study design, perhaps due to their limited inclusion criteria stating meta-analysis was inappropriate. Despite concluding there was a preponderance of well-designed studies, it recommended ESWT after traditional conservative methods had failed. Following this review, higher quality RCTs with robust methodological design began emerging [166]. A systematic review and meta-analysis by Chang et al. [167] of 12 studies including 11,431 patients compared the effectiveness of F-ESWT of different intensities and R-ESWT for PHP. It concluded that using the highest most tolerable energy output within medium intensity ranges is the most superior F-ESWT method and that R-ESWT is a cost-effective efficacious alternative. A systematic review including ten studies on PHP concluded that overall, there is good Level-1 evidence for the effectiveness of F-ESWT, with one study providing Level-1 evidence for R-ESWT [85]. A meta-analysis by Aqil et al. [168] included seven RCTs comparing ESWT with placebo. It concluded that ESWT is safe and effective for PHP unresponsive to other nonoperative treatments, with improved pain scores after 12-weeks and maintained for 12 months. It recommended the use of ESWT for PHP pain, with a minimum of three months failed conservative treatment. A meta-analysis by

Zhiyun Li et al. [169] on F-ESWT and PHP with strict inclusion criteria, included five RCTs. It concluded there was strong evidence that ESWT was effective in treating PHP compared to placebo and recommended its use when conservative interventions fail. A meta-analysis by Dizon et al. [170] included 11 high quality RCTs and concluded that both moderate and high-energy ESWT are effective in treating PHP. A systematic review and meta-analysis by Yin et al. [171] included seven RCTs and concluded ESWT was significantly superior for pain relief and function over control for PHP. It recommended that studies with long-term follow-up are needed to elucidate long-term efficacy. A meta-analysis by Lou et al. [172] included nine RCTs comparing ESWT without local anaesthesia against placebo in PHP treatment. ESWT significantly improved success rates of reduced heel pain, reducing pain by 60% with morning pain and during activities. It concluded ESWT is particularly effective in relieving PHP pain and recommended its use when traditional treatments have failed.

A methodologically robust meta-analysis by Sun et al. [173] included nine high quality RCTs on ESWT and PHP. It concluded that F-ESWT is associated with higher success rates and pain reduction compared to sham in PHP, recommending it when conservative treatment fails. However, the authors acknowledged limitations of the included studies, suggesting further high-quality RCTs with larger sample sizes are warranted. Recently, several systematic reviews with network meta-analysis have compared ESWT versus other conservative PHP treatments, with all finding superior outcomes for ESWT. A recent comprehensive systematic review with network meta-analysis included 31 RCTs comparing effectiveness of all commonly used PHP treatments, with ESWT being ranked the most effective treatment for short, medium and long-term pain and function [174]. A network meta-analysis including 19 RCTs and 1676 participants compared ESWT ultrasound, ultrasound-guided pulsed radiofrequency, intracorporeal pneumatic shock therapy, LLLT and non-invasive interactive neurostimulation for PHP pain relief [175]. Only R-ESWT induced significant pain reduction compared with placebo at six weeks and was the only recommended treatment. Another recent network meta-analysis compared pain relief performance of eight different therapies, including 41 studies and 2,880 patients. ESWT was superior to nonsteroidal anti-inflammatory medications, corticosteroid injections, autologous whole blood, platelet-rich plasma, ultrasound therapy, botulinum toxin A, and dry needling. In terms of one-month, three-month and six-month pain outcomes, only ESWT turned out to be of better efficacy than placebo. For all seven outcomes ESWT ranked first and was recommended as the optimal treatment [176]. Systematic reviews and meta-analysis have also directly compared ESWT versus corticosteroid injections [177-179], and ultrasound [180], with all finding ESWT superior.

6.6 Gluteal tendinopathy

The diagnosis of 'greater trochanteric pain syndrome' has been associated with trochanteric bursitis and inflammation of gluteal tendons [181]. However, the aetiology of gluteal tendinopathy is associated with the degeneration of the gluteal tendons attaching to the greater trochanter [182]. The combination of excessive compression and high tensile loads within these tendons may cause damage [183]. Lateral hip pain with resisted hip abduction, passive adduction and palpation can confirm diagnosis, with hip muscle weakness, altered biomechanics and impaired gait also common [184]. Prevalence in those over age 50 has been reported as high as 18% and is highest in middle aged women, impacting on daily activities, quality of life and causing psychological distress [185]. Exercise and load modification can be successful, but recurrence is common and refractory cases can require surgery [186]. A systematic review of 14 studies on gluteal tendinopathy management concluded there was moderate evidence for ESWT, however they identified a need for better quality RCTs [187]. Similarly, another systematic review on ESWT and lower limb tendinopathy concluded there was moderate evidence ESWT was more effective than other non-operative interventions, recommending it as an alternative treatment [17]. These reviews included the only two good quality RCTs conducted on gluteal tendinopathy, with ESWT composite effectiveness determined to be 78.8% at 12 months [188] and 74% at 15 months [189]. The most recent RCT conducted on gluteal tendinopathy compared F-ESWT with ultrasound in 50 patients, including 44 females [190]. Treatment with F-ESWT was significantly superior to ultrasound for reducing pain measured by p-NRS at both two months (2.08 vs 3.36) and six months (0.79 vs 2.03). There was a significant improvement in physical function in both groups, with neither being statistically superior. Despite these positive findings, the current evidence is limited with further high-quality RCTs needed.

6.7 Hamstring tendinopathy

Proximal hamstring tendinopathy can occur in both the general population and in athletes involved in sports with frequent change of direction movements such as soccer or sagittal plane activities such as hurdling or sprinting [191]. It is not uncommon for the condition to present bilaterally and it is characterised by localized deep pain in the ischial tuberosity region that is often exacerbated after activities such as running, squatting or sitting [192]. There is currently a lack of consensus regarding diagnostic criteria and treatment, with progressive exercise considered the standard treatment approach [193]. Any of the hamstring tendons can be involved, with the biceps femoris tendon (41%) the most implicated [194]. Compression of the tendon at its attachment to the ischial tuberosity during hip flexion and adduction is considered a key etiological factor, leading the condition to be considered as an insertional tendinopathy [195]. The only RCT investigating ESWT for hamstring tendinopathy was conducted with 40 professional athletes, with ESWT compared against conventional physiotherapy including an exercise program over one month [196]. At 3 months after treatment, 17 of the 20 patients (85%) in the ESWT group and two of the 20 patients (10%) in the physiotherapy group achieved a reduction of at least 50% in pain. The authors concluded that ESWT was safe and effective for pain and function in hamstring tendinopathy and was superior to conventional physiotherapy at three, six and twelve months.

7. Controversy and Limitations

Despite the theoretical plausibility and clinical success of ESWT in tendinopathy, a myriad of treatment protocols have been used in studies, with vast variances in treatment delivery methods [197]. Some studies have found no benefit of ESWT; therefore, some controversy exists surrounding its use. However, these poor results may be related to differences in methodology, patient section criteria, device used, energy levels and outcome measures [19]. There are wide variances in treatment sessions used, with some recommending one session and others a standardized model of three sessions [198]. An individualized protocol adapted to patient response, with as many as 11 sessions has also been found feasible and recommended over standardised protocols [199]. Studies have also shown that ESWT is less effective for tendinopathy when administered with local anaesthesia as it inhibits analgesic effects and release of pain mediators with hyperstimulation [172]. The conflicting findings in studies using ESWT for tendinopathy may be explained by variances in study design (patient number, chronic or acute condition, sham group, comparisons with other treatment). Treatment parameters also differ (total energy use, R-ESWT or F-ESWT, low-energy, high-energy, direct or indirect contact, device differences). Differences in outcomes measures are also common (follow-up duration, pain assessment method, use of an algometer or a dolorimeter, objective or subjective assessment of pain, success rate measurement). Controversy over the ESWT type, energy, number of treatment sessions, use of image-guided or clinically guided methods, and the area undergoing ESWT has resulted in uncertainty regarding optimal treatment parameters [166]. These issues should be addressed in future research in order to elucidate the optimal treatment protocols.

In clinical practice, ESWT is rarely used in isolation and is often combined with specific exercises, however, RCTs have generally not adequately addressed this, often comparing ESWT alone with placebo [200]. As monotherapy is not often implemented clinically, there is a need for a comparison of more applicable treatment interventions in future ESWT studies [201]. Current research recommends combined rather than isolated treatments in tendinopathy, and in clinical practice ESWT is often combined with exercise during treatment [202]. However, the majority of RCTs investigating ESWT have used it in isolation, which is not reflective of clinical practice. Recently some studies have found combining ESWT and specific exercise feasible and effective for tendinopathy [147]. However, the optimal treatment protocols for ESWT interventions in isolation or combined with exercise are still undetermined [197]. There is increasing evidence for the clinical effectiveness of ESWT in tendinopathy, but there is still a need for larger and higher quality studies [85]. The most effective treatment protocols need to be determined with future research following clinical practice, where treatment is delivered as comprehensive protocols.

8. Conclusion and recommendations

This review has provided a comprehensive overview of the research to date on ESWT for tendinopathy. Although there are uncertainties regarding optimal treatment parameters and protocols for ESWT in tendinopathy treatment, there is clear evidence of effectiveness for improving pain and function in the seven tendinopathies reviewed. Therefore, ESWT can be recommended as a treatment for PHP, Achilles, patellar, lateral elbow and calcific rotator cuff tendinopathies based on a significant body of evidence including systematic reviews and meta-analysis. Despite the dearth of studies for hamstring and gluteal tendinopathy, RCTs have shown good outcomes and while ESWT can be recommended, further substantive high-quality studies are required in order to make definitive recommendations. When implemented for tendinopathy, ESWT should be administered following currently recommended protocols and parameters to increase likelihood of effectiveness. Further research is required to determine the optimal ESWT protocols for specific tendinopathies, with future studies investigating comprehensive treatment interventions which combine ESWT with other tendinopathy treatments such as exercise, reflective of clinical practice.

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