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Extracorporeal shock wave therapy for the treatment of osteonecrosis and bone vascular diseases: a systematic review of randomized controlled trials

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Abstract. – OBJECTIVE: The aim of the study is to review the available literature on the use of Extracorporeal Shock Wave Therapy (ESWT) for the treatment of osteonecrosis (ON) and bone vascular disease (BVD), to understand its therapeutic potential and compare it with other therapies.

MATERIALS AND METHODS: A systematic review was performed on the PubMed, Scopus, Science Direct, and Research Gate databases with the following inclusion criteria: 1) randomized controlled trials (RCTs); 2) written in English; 3) published in indexed journals within the last 25 years (1995-2020); and 4) dealing with the use of ESWT for the treatment of BVD or ON. The risk of bias was assessed by the Cochrane Risk of Bias tool for RCTs.

RESULTS: Five studies involving 199 patients in total (68 female and 131 male) were included. Patients in the control groups received different treatments, like surgery, bisphosphonates in combination with prostacyclin or ESWT, and hyperbaric oxygen therapy. Looking at the quality of the available literature, none of the studies included could be considered a "good quality" study; only one was ranked as "fair" and the remaining were marked "poor" quality studies. No major complications or serious adverse events were reported in any of the included studies. Based on the available data, ESWT can produce rapid pain relief and functional improvement.

CONCLUSIONS: Overall, a substandard quality of method emerged from the analysis of the literature, with most studies flawed by relevant bias. Ultimately, ESWT has the potential to be a useful conservative treatment in bone degeneration due to vascular and tissue turnover impairment.

Key Words:
Shock wave therapy, Osteonecrosis, Bone vascular disease, Hip, Knee.

Introduction

ESWT was first used for the treatment of kidney stones at the end of the '80s (urological lithotripsy). Gradually, it acquired new fields of application in bone diseases and tendinopathies. Only recently, ESWT showed unexpected therapeutic potential in Regenerative Medicine[1,2]. Early studies[3,4] demonstrated the ability of ESWT to enhance tissue regeneration in non-unions and other healing disorders. Over the years, an increasing number of trials and experimental studies clarified some of the mechanisms of action of this biophysical stimulation (primarily angiogenesis and bone regeneration)[5]. Therefore, new applications were proposed, particularly in the treatment of osteonecrosis (ON) and "Bone Vascular Diseases" (BVD)[6-10]. The latest can be considered a heterogeneous group of painful bone conditions, characterized by altered local remodeling due to impairment of vascular supply. This leads to hypoxic conditions[9] that might result in osteonecrosis (ON). Osteonecrosis induces a severe alteration of the bone microarchitecture causing structural collapse and subsequent osteoarticular degeneration[2].

ON and BVD still represent a clinical challenge: early diagnosis and timely intervention

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seem to be the key points for a successful therapeutic strategy[11]. Magnetic resonance imaging (MRI) examination has the capacity to detect the early stages of altered local bone turnover and, therefore, it creates the opportunity for early intervention[12,13]. Unfortunately, a clear therapeutic algorithm has not been created, yet[14].

As a general agreement, surgery (bone core decompression, bone grafting or any prosthetic replacement) should be considered as the last therapeutic resource. Over the years several conservative-treatments, both pharmacological and biophysical, have emerged with different levels of efficacy[15-17]. First of all, non-weight bearing mobilization should be observed. Then, non-invasive therapies that can positively interfere with abnormal bone turnover, can be taken into consideration. These include: bisphosphonates, hypolipidemic and anticoagulant drugs[18], hyperbaric oxygen therapy, pulsed electromagnetic fields, vasodilators (e.g., prostacyclin), tumor necrosis factor (TNF) inhibitors and focused extracorporeal shock wave therapy (fESWT)[19,20-22]. In recent years, more and more clinical evidence[23] and experimental studies have highlighted the interesting role of ESWT as a conservative approach for the treatment of local tissue degeneration in ON and BVD, appearing as a potential tool to counteract osteoarticular damage and probably prevent higher degrees of joint impairment. On the other hand, methodological difficulties in designing randomized controlled trials and the heterogeneity of available technical instruments and therapeutic protocols are responsible for a deficiency of high-quality clinical studies and scientific evidence on the efficacy and mechanism of ESWT.

The purpose of this paper is to systematically review the best evidence, retrieved from randomized controlled trials, on the safety and efficacy of ESWT for the treatment of BVD and ON, and to identify areas that require further investigation.

Materials and Methods

A systematic review of the literature on the use of focal extracorporeal shock wave therapy treatment for osteonecrosis and vascular bone disease was performed. A search was conducted for articles in English published up until the end of May 2021. PubMed, Scopus, Science Direct, and Research Gate electronic databases were investigated using a combination of ("ESWT" OR "shock wave therapy") AND ("bone marrow oedema" OR "bone marrow edema" OR "osteonecrosis" OR "algodystrophy" OR "complex regional pain" OR "bone vascular disease") as key words. Together with the database search, a reference list screening and monitoring of citations was included to identify any additional studies.

The screening process and analysis were separately conducted by 2 independent observers (CS and MA). First of all, articles were screened looking at title and abstract. The following inclusion criteria for relevant articles that passed the first screening process were used: 1) randomized controlled trials (RCTs); 2) written in English; and 3) published in indexed journals within the past 25 years (1995-2020); 4) dealing with the use of ESWT for the treatment of BVD or ON in accordance with the International Society for Medical Shock wave Treatment (ISMST) recommendations for bone treatments (e.g., the use of a focused high-energy SW source and guided placement technique). Exclusion criteria were: articles written in other languages, reviews, nonrandomized studies or studies examining other applications of ESWT not directly related to BVD or ON. In the second phase, the full texts of the selected articles were looked at with further exclusions according to the previously described criteria. A flow chart of the systematic review is provided in Figure 1. Relevant data were then extracted and included into a single database, with the agreement of both observers, to be analyzed for the purposes of this manuscript. The following data were retrieved: (1) treatment groups, (2) sample size and patient characteristics, (3) method of ESWT administration, (4) treatment protocols adopted, (5) outcome measures, (6) timing of follow-up assessments and (7) summary of clinical outcomes. Each discrepancy was discussed and resolved by the senior investigator (CDA), who made the final judgment. Risk of bias was assessed using the Cochrane Risk of Bias for Randomized Controlled Trials tool, which evaluates seven different types of bias. Each of them was rated "Low Risk", "High Risk", or "Unclear Risk" based on specific criteria. Subsequently, the results of this assessment were converted into AHRQ (Agency for Healthcare Research and Quality) standards, which ultimately classify RCTs into "Good Quality", "Fair Quality", and "Poor Quality".

Results

A total of five studies published between 2005 and 2015 regarding the use of ESWT in the treat-

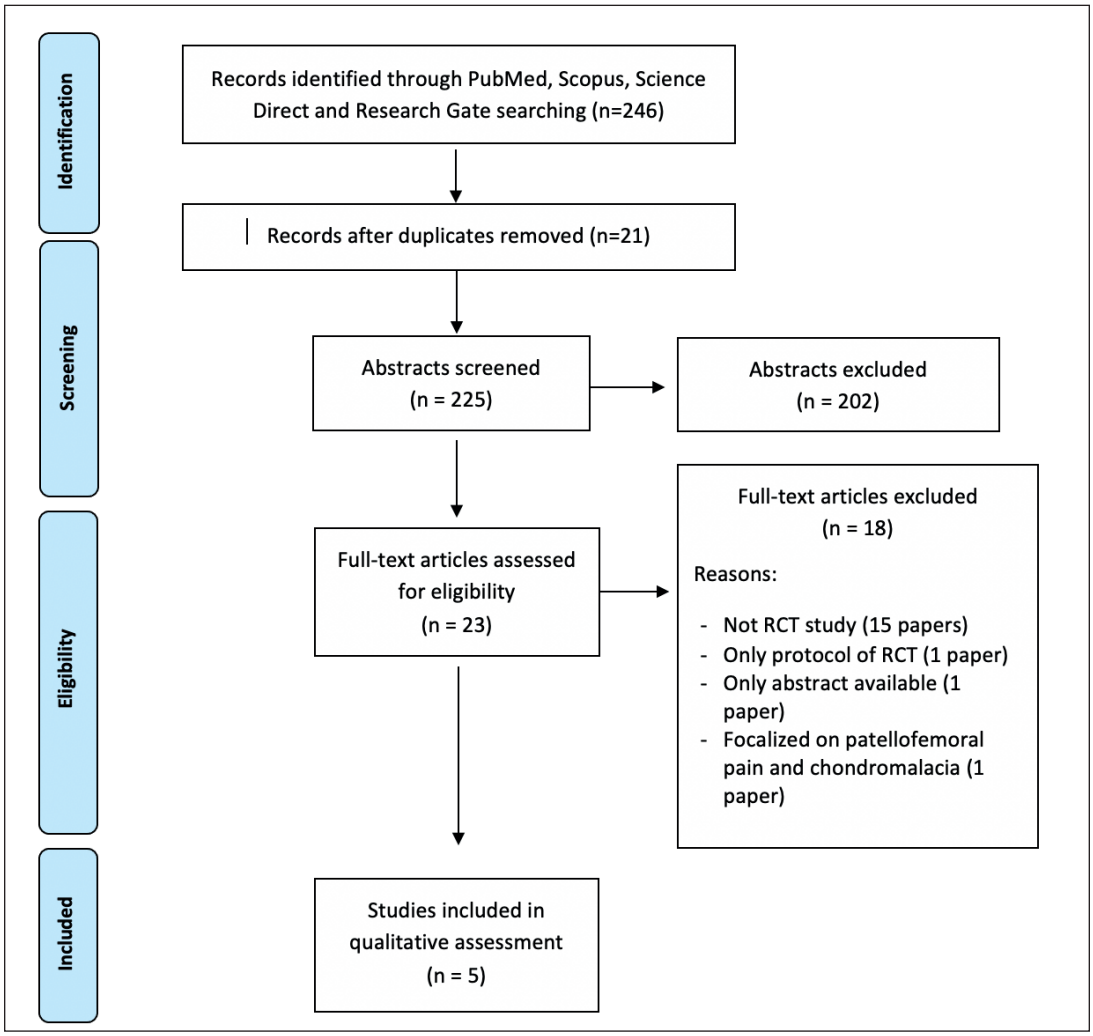

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart resuming the paper's selection process.

ment of vascular bone disease and osteonecrosis were included in this review. Two studies[19,24] were pooled and considered as one study because one represents long-term results of the previous one. A detailed description of each study is provided in Table I.

Study Design and Quality

All studies were, as per inclusion criteria, RCTs. The configuration of the studies was extremely variable: patients in the control groups received different treatments, such as surgery (e.g., core decompression with cancellous bone, non-vascularized autogenous fibula graft)[19,24] or alendronate + prostacyclin[6] and ESWT + alendronate[26]. In one study, ESWT was applied to the control group instead of the study group, which received hyperbaric oxygen therapy + ESWT + alendronate[25]. According to the AHRQ standard, we found that none of the studies selected for this systematic review reached a standard of "Good quality", only one[6] was classified as an RCT of "Fair quality" and the others[19,24-26] were considered of "Poor quality". The results of the analysis performed with the Cochrane Risk of Bias tool for RCTs are detailed in Table II. Regarding the process of generating the random sequence, it was specified in all papers. It was based on odd/even numbers in two studies[19,24], by medical record number in one study[26], by block randomization in another study[6], and by computer-generated random assignment in the remaining study[25]. The allocation concealment method was not described in sufficient detail in three studies[19,24,26]; only in one article did the authors use the sealed envelope method[6]. All articles reported outcomes in full. Regarding the sample size calculation, in all included studies the power analysis meth-

Table I. ESWT for the treatment of BVD and ON: data extracted from RCTs included in the review.

Publication	Study Design	Score	Patients Characteristic	ESWT device	Therapeutic Protocol and follow-up	Results
Wang et al[24] 2012	RCT (ESWT *vs.* core decom -pression)	VAS, Harris Hip Score, ADL activity	48 (23 *vs.* 25) Age: 39.8 *vs.* 39.9 y Sex: 20M:3F *vs.* 23M:2F ONFH: grade 1-3	Electrohydraulic OssaTron High Medical Technology C-arm guided N° and Int: 6000 (1500 x 4 pts) 0.62 mJ/mm²	Single session FU at 6.12 mo + annually till 108 mo (9 yrs)	ESWT appeared to be more effective than core decompression in patients with early-stage osteonecrosis of the femoral head
Wang et al[26] 2008	RCT (ESWT + alendronate *vs.* ESWT)	Need for THA, VAS, Harris Hip Score	48 (25 *vs.* 23) Age: 38.6 *vs.* 35.7 y Sex: 20M:15F *vs.* 13M:10F ONFH: grade 1-3	Electrohydraulic OssaTron Sanuwave C-arm guided N° and Int: 6000 (1500 x 4 pts) 0.62 mJ/mm²	Single session FU at 1, 3, 6, 12 and 24 mo	Significant improvements in both groups. ESWT and alendronate pro-duced similar result as compared with ESWT alone
Hsu et al[25] 2010	RCT (ESWT + HBO + alendro-nate *vs.* ESWT)	VAS, Harris hip score, WOMAC, SF-12 (physical and mental)	63 (28 *vs.* 35) Age: 39.1 *vs.* 39.6 y Sex: 18 M:10F *vs.* 27 M:8F ONFH: grade 1-3	Electrohydraulic OssaTron Sanuwave C-arm guided N° and Int: 6000 (1500 x 4 pts) 0.62 mJ/mm²	Single session FU at 1, 3, 6, 12 and 24 mo	Cocktail therapy is effective for early ONFH; results are comparable to ESWT alone. The joint effects of HBO and alendronate in addition to ESWT were not observed.
Gao et al[55] 2015	RCT (ESWT *vs.* prostacyclin + bisphosphonate)	VAS, WOMAC, SF-36 score	40 (20 *vs.* 20) Age: 41.6 *vs.* 45.1 y Sex: 11M:9F *vs.* 9M:11F BMSE knee	Electromagnetic Dornier Compact DELTA II Rx guided N°: 3000-4000 Fq: 2-3 Hz Pw 0.44 mJ/mm²	Two sessions (1t/wk) FU at 1, 3, 6, 12 mo)	ESWT superior in VAS, WOMAC and SF-36 in every times of follow-up. ESWT produces rapid pain relief and functional improvement.

ADL, activity day living; BMSE, bone marrow edema syndrome; CG, control group; F, female; FQ, frequency, FU, follow-up; HBO, hyperbaric oxygen; INT, intervention; M, male; MO, month; ONFH, Osteonecrosis of femoral head classified according to the Association Research Circulation Osseous (ARCO) classification; PW, power; RCT, randomized controlled trial; SF-12, the 12-Item Short Form Health Survey; SF-36, the 36-Item Short Form Health Survey; SG, study group; T, time; THA, total hip arthroplasty; V, volume; VAS, visual analog scale; WOMAC, arthroplasty; WK, week; Y, years.

Table II. Quality assessment of included studies.

Publication	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Bias	Blinding of Participants and Personnel	Blinding of outcome assessment	Incomplete Outcome Data	AHRQ Standards
Gao et al[55] 2015	Low	Low	Low	Low	Unclear	Unclear	Low	Fair
Wang et al[19,24] 2012 and 2005	Low	High	Low	Unclear	High	Unclear	Low	Poor
Hsu et al[25] 2010	Low	High	Low	Unclear	Unclear	Unclear	Low	Poor
Wang et al[26] 2008	Low	High	Low	Unclear	High	Unclear	Low	Poor

ods were not fully clarified. Blinding of participants or staff was not clear in all studies. In addition, the risk of attrition bias was considered low for all studies. Flow charts describing the patient selection process were reported in only three articles[6,25,26], whereas patient demographic characteristics were present in all articles. At last, we found that only one study was registered in a public registry of clinical trials[6], whereas the others did not mention any registration, which should be mandatory according to the 2010 CONSORT guidelines.

Patients and Evaluation Methods

Five studies[6,19,24-26] involving a total of 199 patients (68 women and 131 men) with ON and BVD met the criteria for inclusion in this review. The mean age was 39.9 years. In three studies[19,24,25], the inclusion criteria included patients with a diagnosis, confirmed by plain radiographs and/or MRI, of stage I, stage II, or stage III ON of the femoral head according to the Association Research Circulation Osseous (ARCO) classification. In only one study the inclusion criterion the presence of a primary bone marrow edema syndrome of the knee (BMESK) was confirmed by MRI examination[6]. Frequent exclusion criteria were patients with acute infections or advanced arthritis, coagulation disorders, cardiac arrhythmia requiring a pacemaker, pregnancy with chronic renal failure, skeletal immaturity or being treated with immunosuppressive drugs for malignancies. Moreover, patients who received any previous treatment demonstrating poor compliance or those who had contraindications to ESWT were also excluded. In the study by Gao et al[6], the finding of avascular necrosis (demarcation) or advanced osteoarthritis (Ahlbäck grade 3 or 4) were considered as exclusion criteria. Preoperative evaluations included a complete history and physical examination, laboratory tests including full blood count, prothrombin time, partial thromboplastin time, blood urea nitrogen and creatinine, plain radiographs and MRI of the affected area (hip or knee). Follow-up evaluations were based on clinical scores, radiographic examinations, and MRI images in all studies. The Visual Analog Scale (VAS) and Harris Hip Score (HHS) were the most commonly used outcome measures. In two studies, the authors used the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the Short Form Health Survey (SF) scores in addition to the clinical scores listed above[6,25].

Treatment

Regarding the application of fESWT, the type of lithotripter used, and the technical details of the clinical application were reported in all studies. All treatments were performed using X-ray guidance. Three studies[19,24,25] used the same treatment protocol: 1,500 pulses at 28 kV, equivalent to an EFD of 0.62 mJ/mm^2, in 4 different areas of the femoral head, for a total of 6,000 pulses, in a single session.

In the BMESK[6] treatment study, patients underwent 3000-4000 pulses of high-energy ESWT (>0.44 mJ/mm^2) at a frequency of 2-3 Hz in two therapy sessions (one week between the two procedures).

Complications

No major complications or serious adverse events were reported in any of the included studies. In all studies, only minor and transient local complications related to ESWT were reported, such as local swelling, small hematomas and bruising that resolved spontaneously with the application of ice packs and observation. On the contrary, other treatments like HBO therapy and alendronate administration caused moderate side effects, such as two cases of transient dizziness and three cases of dyspepsia, respectively[25]. In another work[6], an episode of headache and facial rash after Alprostadil infusion was described in three patients. Additionally, in surgically treated patients, pain at the iliac crest donor site was reported in 58% of patients[19,24].

Reported Clinical Outcome

Wang et al[19,24] conducted an initial study in 2005, followed by another at eight to nine years of follow-up. They concluded that ESWT appears to be more effective than surgery (core decompression and bone grafting) in patients with early-stage osteonecrosis of the femoral head in both the short and long term. Wang et al[19,24] compared the use of ESWT alone and in combination with alendronate in the treatment of early stage ON of the hip. They found comparable results in both treatment groups. Firstly, they concluded that ESWT is effective with or without concomitant use of alendronate and that the joint effects of alendronate in early hip ON are not realized in the short term[26]. An interesting study evaluated the efficacy of a cocktail therapy consisting of ESWT, alendronate and HBO compared with the single use of ESWT in early hip necrosis. After a 2-year follow-up, the results of cocktail thera-

py were comparable to ESWT alone. The combined effects of HBO and alendronate compared with ESWT alone were not observed[25]. Gao et al[6] analyzed the efficacy of ESWT in contrast to a combination treatment that involves the use of intravenous prostacyclin and bisphosphonate for the treatment of BMESK. They demonstrated greater improvement in pain and more rapid regression of bone marrow edema in the ESWT group. The authors concluded that ESWT can produce rapid pain relief and functional improvement.

Discussion

This systematic review highlighted several key findings: 1) the paucity of high-level studies comparing ESWT and other treatments, 2) the promising results of ESWT in providing symptomatic relief and improving function at short- and long-term assessment and 3) the need to develop more high-evidence studies on the topic, looking specifically at the role of combined treatment with shock waves and bisphosphonates.

ESWT might represent a valuable therapeutic tool for enhancing tissue regeneration in various musculoskeletal diseases[27-29]. SW are acoustic waves that when applied to living tissue induce a cascade of biological cellular reactions based on the activation of interconnected biomechanical pathways that ultimately stimulate local tissue regeneration through the secretion of various growth factors[2,30-34]. Although the reactions between "mechanical strain" and cells are still being studied, recent studies emphasize the promotion of angiogenesis[35], a direct effect on "stem cells" at various stages of differentiation and an influence on the innate immunity through an increased macrophage activity[36]. When considering SW actions on bony tissue, a direct effect on the osteoblastic lineage cells at different stages of differentiation was observed[37,38]. It has also been hypothesized a possible effect on the activity of osteoclasts (OCs), whose role in bone turnover is fundamental. Although currently *in vitro*, preliminary studies seem to indicate that SW can reduce the activity of OCs, through the inhibition of osteoclastogenic factors. Moreover, considering that SW can reduce bone marrow edema and pain with a time course similar to that induced after administration of specific drugs, an assumption of a direct action in inhibiting the activity of OCs[39,40] can be formulated. Bone is a highly specialized connective tissue, subject to a continuous remodeling process (resorption/formation). The correct and synchronous functioning of this mechanism in physiological conditions is able to ensure the structural integrity of the subchondral bone architecture at the osteoarticular level[41]. Furthermore, in addition to systemic and metabolic factors, some local agents (including trauma) can negatively affect bone turnover. As a result, a subversion of the trabecular microstructure could occur, leading to possible lasting consequences if not promptly recognized and treated[5]. Histologically, the hallmark feature of altered tissue turnover has been described as accelerated bone remodeling. This is characterized by predominant osteoclastic bone resorption (also known as "Regional Acceleratory Phenomena" or RAP)[42], with a significant component of pathological neoangiogenesis related to exuberant osteoclastic activity triggered by various noxae (including trauma).

The clinical counterpart is represented by the so-called "Bone Vascular Diseases" (BVD), a relatively heterogeneous group of painful bone conditions characterized by an altered local level of remodeling due to the "deficiency" of vascular supply and the resulting hypoxic conditions[10]. This hypoxic state can eventually lead to osteonecrosis. In clinical practice, the most frequent form of BVD is a vascular osteonecrosis of the femoral head, which can be classified as "idiopathic" in approximately 5-25% of cases, whereas 75-90% are secondary to a specific cause[43-45]. Risk factors for secondary forms include: steroid therapy, alcoholism, smoking, previous trauma or surgery on the affected joint/bone, radiation therapy, onco-hematological diseases, bone marrow disease (e.g., Gaucher disease), sickle cell anemia, hypercoagulable blood conditions, systemic lupus erythematosus (SLE), organ transplantation, HIV infection and antiviral drugs (protease inhibitors)[46-48]. If AVN secondary to trauma seems to be directly related to a damage to the external vascular supply, with local hypoxia and consequent weakening/collapse of the subchondral bone, in other cases, the most likely pathogenic mechanism could be due to disseminated intra-vascular coagulation. In fact, among BVD, we now include the so-called "Bone Marrow Edema" (BME)[44]. Originally described as "Bone Marrow Edema Syndrome" of the hip and considered an incomplete form of algodystrophy (due to the absence of skin dystrophy and vasomotor reactions), it is considered by some authors as an unsuccessful form of osteonecrosis, most commonly involving the knee joint[14,49,50].

The treatment of BVD, whose aim is to prevent or slow joint degeneration, still remains a clinical challenge. Various "conservative" strategies have been proposed over the years, both pharmacological and biophysical, with varying levels of evidence on their effectiveness. In addition to non-weight bearing mobilization, a precautionary measure to be observed as a first step, the following approaches have been tested: bisphosphonates, hypolipidemic and anticoagulant drugs, hyperbaric oxygen therapy, pulsed electromagnetic fields, vasodilators (e.g., prostacyclin), tumor necrosis factor (TNF) inhibitors, and extracorporeal focused shock wave therapy (fESWT)[51-54].

Although this review included only randomized controlled trials, critical appraisal revealed relevant biases in all five studies considered, which do not allow to clearly understand how ESWT relates to "standard" approaches currently adopted for BVD and ON. Shock wave therapy was tested in contrast to pharmacological agents, hyperbaric oxygen therapy and surgery. Unfortunately, the low number of studies found, with different clinical scores adopted, did not allow the authors to perform a meta-analysis of the results. Of the five studies considered, four were related to hip pathology and only one to the knee, so it is difficult to draw valid conclusions particularly on the knee. All analyzed papers were characterized by weak power analysis and lack of a statement that clearly elucidates primary outcomes and sample size calculation. As a result, a high risk of underpowered studies is present, with evident consequences for the significance and reliability of the results. Most articles did not report losses to follow-up and their management, blinding and randomization and/or allocation methods when applicable. Hence, it is clear that there was a general lack of adherence to the Consolidated Standards of Reporting Trials guidelines for reporting methods and outcomes in RCTs, and therefore, none of the included studies could be rated as a "good quality" RCT according to the Agency for Healthcare Research and Quality standard.

However, despite the relevant methodological limitations mentioned above, some clinical considerations can be drawn from the literature review, which highlights overall promising results of ESWT in reducing pain and improving functional status in patients with BVD and ON. First of all, this review added further confirmation that this therapy can be safely utilized on bone even at high energy, without fear of major side effects. As a matter of fact, no major complications or serious adverse reactions were reported in any of the included studies (199 patients in total). A rate of 41.9% developed only mild local swelling, small hematomas and bruising, which resolved spontaneously with the application of ice packs and observation. Given the limited clinical relevance and the short duration, these can be considered negligible side effects related to the application of high-energy ESWT. These are not at all worthy of comparison to the possible general discomforts related for example to pharmacological therapies or to surgery. Moreover, if we extend the evaluation to other scientific articles on the subject, not included in this review for the reasons listed above, on a total of more than 500 patients, the percentage of mild side effects does not exceed 35%[55]. Mean follow-up was performed in the short to medium term (1 month to 2 years), with one study reporting data up to 9 years. Based on these data, we can speculate that ESWT might provide positive results in terms of symptomatic relief as early as 1 month after treatment in patients with bone edema and after approximately 3 months in patients with early stage ON. These effects appear to continue over the long term.

When it comes to comparing the efficacy of ESWT and other treatments, the aforementioned poor quality of RCTs has a profound (negative) impact on the reliability of the results. An interesting aspect that emerged from the review is related to the use of combined treatment with ESWT and bisphosphonates. We hypothesized that these two therapies might have a synergistic effect in the treatment of bone edema and osteonecrosis through their different mechanisms of action. ESWT is able to promote blood supply to the femoral head through induction of neovascularization, whereas bisphosphonates might improve bone quality by inhibiting osteoclast activity. Considering the studies in the review, it appears that the concomitant use of bisphosphonates and ESWT is not superior in terms of efficacy to treatment with ESWT alone. Similarly, the contemporary use of the hyperbaric chamber and ESWT does not appear to be superior to ESWT alone.

Limitations

The present manuscript has some limitations. Firstly, a meta-analysis of the data was not performed: the only possible attempt in this regard would have been to compare ESWT with bisphosphonates, but the low number of studies and low homogeneity of the data would have led to an

unreliable evaluation. Additionally, although this is a systematic review of RCTs, the low number and modest quality of the studies does not allow to define clear indications on the comparative effectiveness of ESWT weighed against other approaches, thus preventing to obtain "practical" guidelines to be adopted in daily practice. Finally, of the five studies considered, four were related to hip osteonecrosis and only one to knee bone edema, which therefore must still be considered an unexplored area of research regarding the application of ESWT.

Conclusions

This systematic review highlighted the current paucity of high-level evidence supporting the use of ESWT in ON and BVD. Factors related to disease complexity, technical limitations regarding equipment and methodological difficulties in performing well-designed RCTs can all be considered responsible for this inadequacy. However, ESWT has been demonstrated to have promising results in counteracting "bone degeneration" related to local alteration of vascular and tissue turnover. Moreover, being a safe and non-invasive approach, it could be applied in combination with other pharmacological and biophysical therapies to achieve a beneficial synergistic effect.

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Conflicts of Interest
The authors declare no conflicts of interest.

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