Extracorporeal shock wave treatment for post-surgical fracture nonunion: Insight into its mechanism, efficacy, safety and prognostic factors (Review)

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Abstract. Post-surgical fracture nonunion (PSFN) represents the failure to achieve cortical continuity at radiological examination after an orthopedic operation, which causes a considerable disease burden in patients with fractures. As one of the traditional treatment modalities, surgical therapy is associated with a high fracture union rate; however, post-surgical complications are not negligible. Therefore, less invasive therapies are needed to improve the prognosis of patients with PSFN. Extracorporeal shock wave treatment (ESWT) is a noninvasive method that presents a similar efficacy profile and favorable safety profile compared with surgical treatment. However, the application and detailed mechanism of ESWT in patients with PSFN remain unclear. The present review focuses on the mechanism, efficacy, safety and prognostic factors of ESWT in patients with PSFN, aiming to provide a theoretical basis for its application and improve the prognosis of these patients.

Contents

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1. Introduction

Post-surgical fracture nonunion (PSFN) is defined as failure to achieve cortical continuity at the fracture site as determined by radiological examination at 6-9 months after the orthopedic operation (such as osteotomies and arthrodesis), and had a prevalence of 4.9-6.8% in patients with fracture during 2011-2019 (1,2). PSFN causes a considerable disease burden in patients with fractures, including long-term chronic pain, leading to disability and reducing the quality of life. Furthermore, it may be associated with an increased risk of death (3-6). Currently, the most commonly used treatment modalities for patients with PSFN include drug therapy (such as skeleton growth factor and teriparatide) and surgical therapy (autogenous bone grafting and internal fixation surgery), with surgical therapy being regarded as the gold standard (7-9). Although the union rate is as high as 70.4-89.2% (reported in different countries during 2011-2021) after surgical intervention, a non-negligible proportion of patients with PSFN still face post-surgical complications due to its invasiveness (10-12). Therefore, less invasive methods are needed to improve the prognosis of patients with PSFN.

Extracorporeal shock wave treatment (ESWT) is a treatment modality that converts the acoustic pulses to a shock wave, and it delivers these short and intense acoustic energy impulses into the targeted bone fracture site through skin and superficial tissues, which then convert into the kinetic energy and exert their therapeutic effect (13-15). Previous studies have reported the efficacy of ESWT in treating patients with fracture nonunion (14,15). For instance, a randomized controlled trial enrolled 126 patients with long-bone nonunions and these patients received ESWT or surgical treatment (including intramedullary nail fixation, plate fixation and combined nail and plate fixation), and this study indicated that ESWT could achieve similar union rates compared with that achieved with surgical therapy (71 vs. 74%) (14). In another study, ESWT induced a union rate of 73% in patients with fracture nonunion, which was similar to that observed in patients receiving surgical treatment (15). However, to the best of our knowledge, there are no studies that comprehensively evaluated the rationale, mechanism and implementation of ESWT in patients with PSFN, thus the present review aimed to address this issue.

2. Mechanisms of ESWT in treating patients with PSFN

Restart of the union procedure. The concept of ESWT is as follows: The acoustic pulses are converted to a shock wave by the lithotripter, and the shock wave can propagate (the propagation of the shock wave in the media may be described as the propagation of sound in the media) in all types of media (including human soft tissue and bone). However, due to the different acoustic impedance of various media, its attenuation varies. If the acoustic impedance (which may be described as the resistance faced by the shock wave during the transmission of the medium; a higher acoustic impedance is associated with a higher resistance faced by the shock wave) is different at the interface of two substances, attenuation will occur at the interface, which may convert to other energies (such as kinetic energy). When a shock wave passes through human tissues, its energy is not easily absorbed by superficial tissues (such as the fat layer and muscle), but can directly reach the bone tissue. In the process of transmission to bone tissue, acoustic energy is lost, and part of the lost acoustic energy is converted to kinetic energy, which causes bone tissue damage and may further restart the bone union procedure (16). It has been reported that ESWT can deliver a high-energy shock wave within a short life cycle (~10 msec) to the targeted bone fracture site (17), thus ESWT can affect the bone tissue without damaging the soft tissues. ESWT can cause tear and shear forces at transition sites, leading to the formation of microfractures at the targeted fracture site and dividing the bone with sclerosis into minor bone fragments (0.1-3.0 mm^3). Finally, the small bone fragments can fill the fracture site, acting as an autologous bone graft (18). At the same time, local bleeding can occur at the microfracture site followed by formation of hematoma, thereby restarting the fracture trauma, aggravating inflammatory responses, releasing various inflammatory cytokines (such as IL-1β and IL-6) and recruiting osteoblasts. Consequently, the bone healing process may be restarted (19,20).

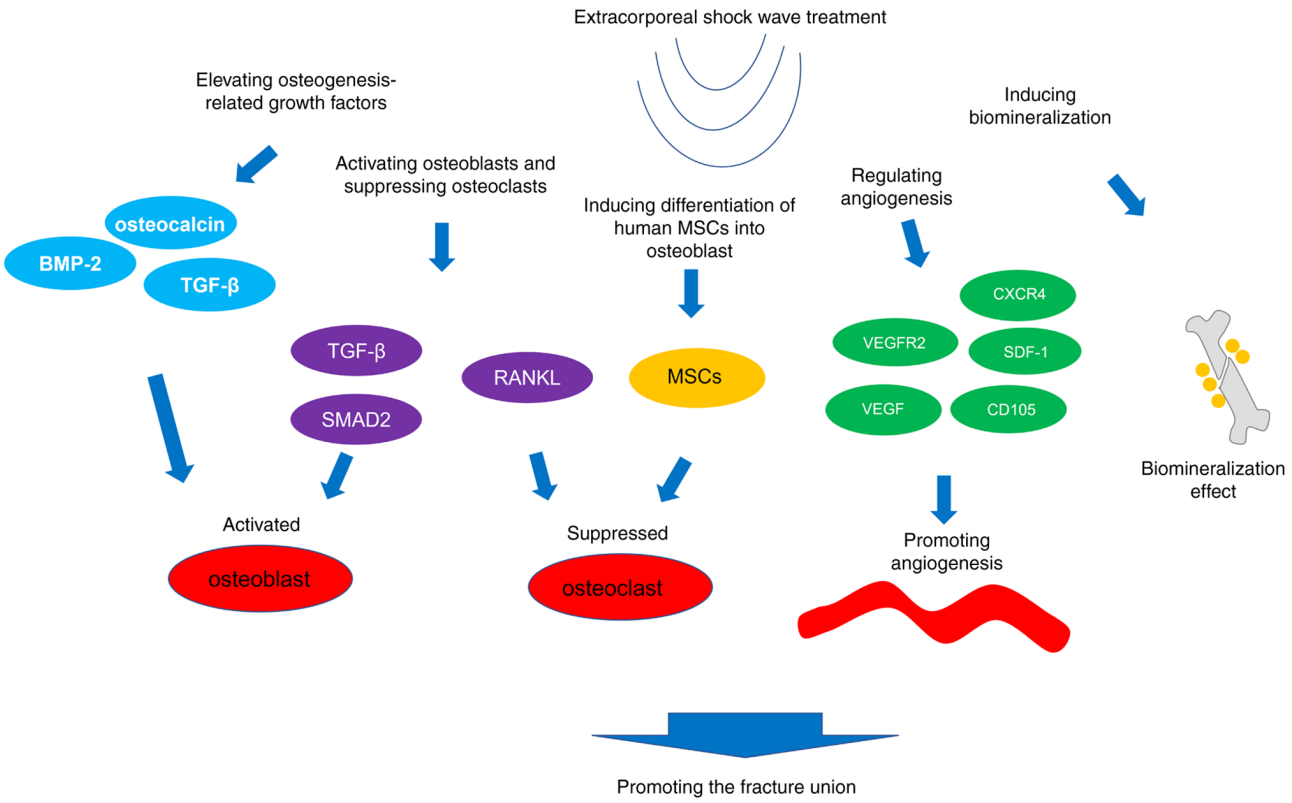
At present, two types of ESWT are commonly applied: Focused ESWT (fESWT) and radial ESWT (rESWT). The former converts the acoustic pulses to a focused acoustic pressure shock wave, creating a high-pressure spot at the targeted fracture nonunion site, while the latter produces stress waves by striking the metal applicator, affecting the targeted fracture nonunion (13). There are some differences between the fESWT and rESWT: i) fESWT can lead to a higher speed of velocity of the wave in the soft tissue, while the speed of rESWT is slower (21); ii) the pressure of f-ESWT would rise in a sharp manner during a very short period, while the pressure of r-ESWT would increase in a linear manner with a long rise time duration; and iii) the wave from fESWT is more focused on the target tissue than that of rESWT, which makes it easier to reach the lesion at depth. Therefore, fESWT is more frequently used in treating bone pathology with deep penetration; in addition, it applies high-energy shock waves and anesthesia is commonly needed (21,22). By contrast, rESWT involves mid-low-energy shock waves, which are frequently used in patients with soft tissue disease (such as carpal tunnel syndrome) (13,23) and lately for treating fracture nonunion of superficial bones (such as navicular bone and tibia) (24,25).

Promotion of osteogenesis-related growth factors. ESWT can promote fracture union via some osteogenesis-related growth factors such as bone morphogenic protein 2 (BMP-2), osteocalcin and TGF-β (26-28). For instance, an *in vivo* study demonstrated that ESWT could achieve improved tibia healing and fracture remodeling, and increase bone mineral density values and the bone tissue formation by regulating the VEGF, van Willebrand factor, proliferation cell nuclear antigen, BMP-2 and osteocalcin released by the osteoprogenitors (26). Another study showed that ESWT could improve mineral density, induce bone formation and increase the expression of type I collagen and osteocalcin (27). Furthermore, the ESWT has also been reported to be involved in the regulation of osteogenesis-related growth factors, such as TGF-β, which further participates in the fracture union (Fig. 1) (28).

Activation of osteoblasts and deactivation of osteoclasts. ESWT regulates osteoblast differentiation and maturation through several pathways, such as the TGF-β/SMAD2 signaling pathway (29), and the differentiation and maturation of the osteoblasts is reported to be associated with new bone formation and development (29,30). Furthermore, it has been reported that ESWT promotes the differentiation of chondroblasts both *in vivo* and *in vitro*, which further induces endochondral ossification and implies its potential in facilitating fracture union (31).

In addition, another study established an osteoporosis rat model and treated the rats with ESWT, finding that ESWT could suppress the osteoclast activity and further promote bone healing (32-34) (Fig. 1). During this process, the actin-bundling protein L-plastin (LPL) may serve a fundamental role. It has been reported that LPL may be regulated following the regulation effect of receptor activator of NF-κB on the PI3K/AKT/specific protein 1, and the deletion of LPL may inhibit preosteoclast fusion by regulating the formation of filopodia, which further participate in the bone union procedure (35).

Differentiation of human mesenchymal stem cells (MSCs). Chen *et al* (36) demonstrated that ESWT promoted the proliferation, survival and migration of MSCs. In addition, the same study revealed that ESWT was also involved in osteogenic differentiation through several mechanisms such as: i) Enhancement of the activity of alkaline phosphatase; and ii) regulation of the expression of runt-related transcription factor-2, type I collagen, osteocalcin and osteopontin. In another study, ESWT with 0.4-mJ/mm^2 energy flux density was able to double the proliferation rate of MSCs (37). At the same time, ESWT also enhanced the differentiation of MSCs into osteoblasts, which implied its potential role in promoting fracture union (37). Chen *et al* (38) performed an *in vitro* experiment in which bone marrow-derived MSCs were treated with ESWT, and found that ESWT could stimulate the proliferation and osteogenic differentiation of bone marrow-derived MSCs (Fig. 1). Further *in vivo* experiments in the same study revealed that seeding ESWT-treated MSCs on poly-lactic-co-glycolic acid scaffolds could induce faster bone formation with more mineral apposition inside the defect site compared with that of MSCs only (38).



Abbreviation: BMP-2, bone morphogenic protein 2; TGF-β, transforming growth factor-β; SMAD2, small Mothers against decapentaplegic homolog 2; RANKL, receptor activator of nuclear factor-κB ligand; MCS, mesenchymal stem cells; CXCR4, C-X-C chemokine receptor type 4; VEGFR2, vascular endothelial growth factor receptor 2; SDF-1, stromal cell-derived factor 1;

Figure 1. Hypothetical flow diagram of ESWT in the treatment of patients with post-surgical fracture nonunion. ESWT, extracorporeal shock wave treatment; BMP-2, bone morphogenic protein 2; RANKL, receptor activator of NF-κB ligand; MSCs, mesenchymal stem cells; CXCR4, C-X-C chemokine receptor type 4; SDF-1, stromal cell derived factor-1.

Angiogenesis. Angiogenesis serves an essential role in fracture union (39,40). A recent study revealed that ESWT could increase the protein expression levels of cell angiogenesis receptor VEGFR2 and angiogenesis biomarkers (VEGF/C-X-C chemokine receptor type 4/stromal cell derived factor-1 axis) (41). Another study, which involved an *in vivo* mouse model with skin wounds treated with ESWT, indicated that ESWT could promote wound healing through regeneration of microcirculation and angiogenesis. In addition, a higher ESWT pulse was associated with an improved recovery effect (42). Furthermore, Modena *et al* (43) suggested that ESWT could activate angiogenesis by upregulating the angiogenesis markers (CD105 and VEGF) (Fig. 1).

Biomineralization. Sternecker *et al* (44) treated zebra mussel *Dreissena polymorpha* with ESWT and analyzed the biological response to evaluate the molecular mechanism of newly formed mineralized tissue after ESWT. The study found that ESWT with a 0.4 mJ/mm^2 energy density could achieve an increment of bone mineralization compared with the control. This finding was further supported by a recent study that proposed a positive association between ESWT energy and the fluorescence intensity of the mineralized tissue (45). The two aforementioned studies suggested that ESWT promoted fracture union by inducing biomineralization (Fig. 1).

Others. Although there is still no definite conclusion, some studies have focused on the mechanism of ESWT on the musculoskeletal and neuromuscular system (46-48). ESWT could alter the elasticity and extensibility of the muscle, which would further benefit the bone union (49,50). However, more studies are needed for further exploration.

3. Efficacy and safety of ESWT in treating patients with PSFN

ESWT monotherapy. In 2001, Rompe *et al* (51) performed a study on 42 patients with PSFN who were previously treated with pseudarthroses after fracture or corrective osteotomies. All patients received fESWT with 3,000 impulses at 0.6 mJ/mm^2 energy flux density for 50-75 min after local anesthesia with a bone union rate of 72.0% at 9 months after fESWT. Furthermore, Elster *et al* (52) re-evaluated the efficacy of fESWT in 172 patients with PSFN who underwent bone fixation (including external, internal or intramedullary fixation, casting, plaster cast, bone graft and autograft). The patients with PSFN received fESWT with a median impulse number of 4,000 at 0.38-0.40 mJ/mm^2 energy flux density for 20-60 min after general or local anesthesia. The results indicated a fracture union rate of 80.2% after a mean follow-up of 4.8±4.0 months (from the first fESWT to the fracture union).

The wide application of fESWT for the treatment of patients with PSFN allowed for the efficiency of rESWT in patients with PSFN to be further recognized and revealed. In 2013, Zhang *et al* (53) studied 42 patients with PSFN who previously received external, internal or intramedullary fixation. The patients were treated with rESWT at different shock dosages and it was found that the rESWT with 1,000 impulses of shock waves group exhibited a fracture union rate of only 28.6%, which was lower compared with that in patients with PSFN receiving rESWT with 2,000 (85.7%) and 3,000 (78.6%) impulses of shock waves. Based on these findings, the use of an rESWT dosage of <2,000 impulses of shock waves was excluded from subsequent clinical trials. In 2017, Kertzman *et al* (24) reported that the rESWT with 3,000 impulses of shock waves at 0.18 mJ/mm^2 energy flux density per session could achieve a fracture union rate of 72.7% at 6 months after rESWT in patients with PSFN who were previously treated with internal plates, nails or intramedullary/internal screw fixations. Furthermore, a recent case report also showed the efficacy of rESWT with 3,000 impulses of shock waves in a patient with PSFN (25). Studies reporting the efficacy of ESWT in patients with PSFN are summarized in Table I.

ESWT vs. surgical treatment. The aforementioned surgical treatment (including external, internal or intramedullary fixation, casting, plaster cast, bone graft and autograft) is regarded as the gold standard for the treatment of patients with PSFN (7-9). Therefore, some studies have also compared the efficacy of ESWT with that of surgical treatment in patients with PSFN (14,16,54). In a study by Cacchio *et al* (14), a total of 126 patients with PSFN were enrolled and treated with fESWT at 4,000 impulses of shock waves at 0.40-0.70 mJ/mm^2 energy flux density or with surgical treatment. A fracture union rate of 70-71% was reported in the fESWT group, which was similar to that in the surgical treatment group (73%) (14). Huang *et al* (54) compared the efficacy of rESWT with that of autogenous bone grafting in patients with PSFN and showed that three sessions of rESWT (3,000 impulses at 80-120 J) with 7-day intervals could achieve a fracture union rate of 87.2%, which was similar to the fracture union rate recorded in patients with PSFN receiving autogenous bone grafting (93.9%).

Furthermore, another study applied a more intensive ESWT method and compared the efficacy of this intensive method with that of surgical treatment in patients with PSFN (16). In detail, a total of 65 patients with PSFN who were previously treated with open reduction and internal fixation were enrolled. fESWT or intramedullary nailing were applied in patients with PSFN. In the fESWT group, all patients received three courses of fESWT. At each course, these patients received the fESWT for 10 min each, twice a week, for up to 4 weeks. The patients in the surgical group received the normal intramedullary nailing surgical treatment instead. The study found that the fracture union rate could increase to 97.0% in the fESWT group, which was higher compared with that in the surgical group (75.0%) (16) (Table I).

ESWT combined with other treatment modalities. Wang *et al* (55) compared the efficacy of fESWT combined with bone marrow grafting with fESWT alone in 42 patients with PSFN previously treated with external, internal or intramedullary fixation. fESWT with 2,000 impulses plus the autologous bone marrow grafting could achieve a fracture union rate of 84.2%, which was numerically but not statistically significantly higher compared with that in patients with PSFN receiving fESWT monotherapy (82.6%). Jin *et al* (56) determined the efficacy of rESWT with autologous cell growth factor injection. rESWT with 3,000 impulses and 0.54 mJ/mm^2 energy flux density plus autologous cell growth factor injection could achieve a fracture union rate of 95.8%, which was higher compared with that in the rESWT group (75.0%) (Table I).

Safety. The safety profile of ESWT in patients with PSFN is generally considered acceptable (14,16,24,51,54). The most common adverse events (AEs) include skin- and blood-related AEs such as local edema, subcutaneous hematoma and peripheral blood vessel damage (14,16,24,51,54). Only a minor proportion of patients report pain (24). In addition to the common AEs, certain patients with PSFN may suffer from infection, blisters and skin ulceration (16,54). The safety profile of ESWT in PSFN is summarized in Table II.

4. Prognostic factors for patients with PSFN

Prognostic factors of fracture union in PSFN. Certain studies have explored the predictive factors for fracture union in patients with PSFN receiving secondary surgery (57-61). These prognostic factors mainly focused on demographic characteristics (such as tobacco usage) and the recovery status of the fracture nonunion (including the dislocation distance, nonunion site and the occurrence of callus in the cortex) (57-61). In a study by Gvozdenovic *et al* (57), patients with PSFN and minor dislocation (vs. those PSFN with greater dislocation) at the union site exhibited a higher fracture union rate after the second surgical treatment. In a study by Konda *et al* (59), lower extremity nonunion, tobacco use, worker's compensation insurance (which is associated with longer time to return to work and worse functional outcomes following the surgery), radiographic bone loss and preoperative short musculoskeletal function assessment function index were associated with fracture nonunion in patients with PSFN. In patients with PSFN and femoral neck nonunion, the predictive factors for revision surgery included a higher preoperative neck shortening ratio (60). In a study by Christiano *et al* (61), the presentation of the callus and the invisible fracture line in the cortex could also predict fracture nonunion.

A recent study established a model based on contrast-enhanced ultrasound that was applied to predict the union rate for patients with PSFN. The study showed that the peak enhancement, wash-in area under the curve (defined as the integral of the signal intensity over time until peak enhancement is reached) and wash-in perfusion index (defined as the ratio of wash-in area under the curve to rise time) at the nonunion site were increased in patients with PSFN and fracture union compared with those in patients with PSFN and fracture nonunion (60).

Prognostic factors of ESWT in treating fracture union in PSFN. Although only a small number of studies have

Table I. Information on the studies reporting the efficacy of ESWT in patients with post-surgical fracture nonunion.

A, Efficacy of ESWT monotherapy

First author/s, year	Study type	No. of cases	Previous surgery type for fracture	Treatment modality		Fracture union rate		(Refs.)
				Intervention	Control	Intervention	Control	
Rompe *et al*, 2001	Cohort	42	Pseudarthroses after fracture or corrective osteotomies	fESWT	-	72.0% (31/43)	-	(51)
Elster *et al*, 2009	Cohort	172	Fixation (including external, internal or intramedullary fixation, casting, plaster cast, bone graft and autograft)	fESWT	-	80.2% (138/172)	-	(52)
Zhang *et al*, 2013	Cohort	42	External, internal or intramedullary fixation	rESWT with 1,000 (group 1) and 2,000 (group 2) shock dosages	rESWT with 3,000 shock dosages	Group 1, 28.6% (4/14); and group 2, 85.7% (12/14)	78.6% (11/14)	(53)
Kertzman *et al*, 2017	Cohort	22	Internal plates, nails and intramedullary/ internal screw fixations	rESWT	-	72.7% (16/22)	-	(24)
Yue *et al*, 2021	Case report	1	Intramedullary nailing	rESWT	-	100.0% (1/1)	-	(25)

B, ESWT compared with surgical treatment

First author/s, year	Study type	No. of cases	Previous surgery type for fracture	Treatment modality		Fracture union rate		(Refs.)
				Intervention	Control	Intervention	Control	
Cacchio *et al*, 2009	RCT	126	Orthopedic operation	Group 1, fESWT with Dornier lithotripter; and group 2, fESWT with Storz lithotripter	Surgical treatment	Group 1, 70.0% (26/37); and group 2, 71.0% (27/38)	73.0% (28/38)	(14)
Huang *et al*, 2015	RCT	72	External, intramedullary fixation	rESWT	Autogenous bone grafting	87.2% (31/35)	93.9% (29/31)	(54)
Wu *et al*, 2021	RCT	65	Intramedullary nailing	fESWT	Intramedullary nailing	97.0% (32/33)	75.0% (24/32)	(16)

C, ESWT combined with other therapy compared with ESWT monotherapy

First author/s, year	Study type	No. of cases	Previous surgery type for fracture	Treatment modality		Fracture union rate		(Refs.)
				Intervention	Control	Intervention	Control	
Wang *et al*, 2006	Cohort	42	External, internal or intramedullary fixation	fESWT with bone marrow grafting	fESWT	84.2% (16/19)	82.6% (19/23)	(55)

Table I. Continued.

C, ESWT combined with other therapy compared with ESWT monotherapy

First author/s, year	Study type	No. of cases	Previous surgery type for fracture	Treatment modality		Fracture union rate		(Refs.)
				Intervention	Control	Intervention	Control	
Jin *et al*, 2018	RCT	48	Open reduction and internal fixation	rESWT with autologous cell growth factor injection	rESWT	95.8% (23/24)	75.0% (18/24)	(56)

ESWT, extracorporeal shock wave treatment; rESWT, radial ESWT; fESWT, focused ESWT; RCT, randomized controlled trial.

Table II. Safety profile of ESWT in patients with post-surgical fracture nonunion.

First author/s, year	ESWT type	Common AEs	(Refs.)
Rompe *et al*, 2001	fESWT	Transient local hematoma	(51)
Elster *et al*, 2009	fESWT	Dose-related local edema, cutaneous petechial hemorrhage and subcutaneous hematoma	(52)
Zhang *et al*, 2013	rESWT	N/R	(53)
Kertzman *et al*, 2017	rESWT	Pain	(24)
Yue *et al*, 2021	rESWT	None	(25)
Cacchio *et al*, 2009	fESWT	Hematomas	(14)
Huang *et al*, 2015	rESWT	Local edema, subcutaneous hematoma and blisters	(54)
Wu *et al*, 2021	fESWT	Local edema, infection, skin ulceration, peripheral blood vessel damage and peripheral nerve damage	(16)
Wang *et al*, 2006	fESWT	None	(55)
Jin *et al*, 2018	rESWT	N/R	(56)

AEs, adverse events; ESWT, extracorporeal shock wave treatment; rESWT, radial ESWT; fESWT, focused ESWT; N/R, not reported.

reported the predictive factors for fracture union in patients with PSFN receiving ESWT, previous evidence has revealed that the shock wave treatment (vs. no treatment) was associated with an increased union rate in patients with PSFN (24,52,62). In addition, a shorter time between fracture and first shock wave treatment, a shorter interval between the fracture and the surgery, a good intramedullary stabilization, and an increased number of extracorporeal shock wave therapy treatments were associated with a higher fracture union rate (24,52,62).

5. Prospects and limitations

Apart from ESWT, several studies have reported advances of the treatment in bone regeneration, such as bone organoid, physical and chemical crosslinked hydrogels, polyether-ether-ketone (PEEK) and double-network metallo-polymer hydrogels (63-66). For instance, one study reported that the bone organoid was constructed *in vitro*, which could simulate the biological function of organs *in vivo*, and a potential strategy for the construction of bone organoids and their application in bone reconstruction was described (63). Another study clarified that biomimetic hydrogels with injectability and compatibility may serve an essential role in bone defect reconstruction, benefiting from their numerous advantages, such as extensive selectivity, rapid gel-forming capacity, tunable mechanical properties and good biocompatibility (64).

However, several challenges should be considered before the aforemetioned advances of the treatment's broad application, such as the poor bonding of PEEK with bone and soft tissue (65). In terms of the ESWT, several limitations should also be noted: i) ESWT has a dose-dependent efficacy but an excessive dose would lead to excessive damage, while an insufficient dose would not reach the optimal efficacy, thus finding the optimal dose is a critical issue that clinicians should consider (53); ii) its effect on other tissues and organs should be studied more extensively; and iii) the construction of ESWT equipment deserves further study. Hence, for the more wide application of these advance methods (including the ESWT) in the treatment of PSFN, more studies are still needed.

6. Summary

Previous studies have reported that ESWT is able to promote fracture union in patients with PSFN (14,16,54). However, to the best of our knowledge, none of these studies comprehensively evaluated the mechanism, implementation and prognostic factors of ESWT in patients with PSFN. The present review aimed to clarify the potential mechanism for ESWT in promoting the fracture union, which mainly includes: i) Restart of the bone union process; ii) activation of osteoblasts and suppression of osteoclasts by elevating osteogenesis-related growth factors, such as BMP-2 and TGF-β, promoting several pathways, such as the TGF-β/SMAD2 signaling pathway, and inducing the differentiation of human MSCs into osteoblasts; iii) promotion of angiogenesis; and iv) biomineralization induction. The present review summarizes the efficacy and safety of ESWT in patients with PSFN, showing that ESWT was effective and tolerable. Furthermore, the current review considered the potential prognostic factors for the facture nonunion and efficacy of ESWT in patients with PSFN, which mainly included demographic characteristics, such as tobacco usage, recovery status of the fracture nonunion, time interval between fracture and first shock wave treatment or surgery, and intramedullary stabilization status. These findings could provide a theoretical basis for orthopedics specialists to improve individualized treatments and the application of ESWT in clinical practice for patients with PSFN. Further high-quality studies are required to validate these findings.

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Authors' contributions

HW contributed to the study conception and design. HW and YS drafted and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zura R, Watson JT, Einhorn T, Mehta S, Della Rocca GJ, Xiong Z, Wang Z, Jones J and Steen RG: An inception cohort analysis to predict nonunion in tibia and 17 other fracture locations. Injury 48: 1194-1203, 2017.
2. Tian R, Zheng F, Zhao W, Zhang Y, Yuan J, Zhang B and Li L: Prevalence and influencing factors of nonunion in patients with tibial fracture: Systematic review and meta-analysis. J Orthop Surg Res 15: 377, 2020.
3. Lerner RK, Esterhai JL Jr, Polomano RC, Cheatle MD and Heppenstall RB: Quality of life assessment of patients with posttraumatic fracture nonunion, chronic refractory osteomyelitis, and lower-extremity amputation. Clin Orthop Relat Res (295) 28-36, 1993.
4. Zura R, Braid-Forbes MJ, Jeray K, Mehta S, Einhorn TA, Watson JT, Della Rocca GJ, Forbes K and Steen RG: Bone fracture nonunion rate decreases with increasing age: A prospective inception cohort study. Bone 95: 26-32, 2017.
5. Yin Y, Xu K, Zhang N, Yi Z, Liu B and Chen S: Clinical and epidemiological features of scaphoid fracture nonunion: A hospital-based study in Beijing, China. Orthop Surg 14: 2455-2461, 2022.
6. Van Wijck SFM, Van Lieshout EMM, Prins JTH, Verhofstad MHJ, Van Huijstee PJ, Vermeulen J and Wijffels MME: Outcome after surgical stabilization of symptomatic rib fracture nonunion: A multicenter retrospective case series. Eur J Trauma Emerg Surg 48: 2783-2793, 2022.
7. Ho CH, Tzeng SC, Farn CJ and Lee CC: Teriparatide as an effective nonsurgical treatment for a patient with basicervical peritrochanteric fracture Nonunion-A case report. Medicina (Kaunas) 58: 983, 2022.
8. Kumaran A and Soh HL: Management of nonunion and malunion after primary mandibular condylar fracture treatment: A review and recommendations. J Oral Maxillofac Surg 78: 2267-2272, 2020.
9. Neumann MV, Zwingmann J, Jaeger M, Hammer TO and Sudkamp NP: Non-Union in upper limb fractures-clinical evaluation and treatment options. Acta Chir Orthop Traumatol Cech 83: 223-230, 2016.
10. Rao BM, Stokey P, Tanios M, Liu J and Ebraheim NA: A systematic review of the surgical outcomes of interprosthetic femur fractures. J Orthop 33: 105-111, 2022.
11. Yang S, Yang Y, Huo Y, Yu J, Sheng L, Sun X, Liu X, Yin J and Yin Z: Effect of the degree of displacement of the third fragment on healing of femoral shaft fracture treated by intramedullary nailing. J Orthop Surg Res 17: 380, 2022.
12. Lari A, Kashif S and AlMukaimi A: Arthroscopic retrograde intramedullary nailing of periprosthetic fractures after total knee arthroplasty-technique, safety, and outcomes. Arthroplast Today 17: 47-52, 2022.
13. Kwok IHY, Ieong E, Aljalahma MA, Haldar A and Welck M: Extracorporeal shock wave treatment in foot and ankle fracture non-unions-A review. Foot (Edinb) 51: 101889, 2022.
14. Cacchio A, Giordano L, Colafarina O, Rompe JD, Tavernese E, Ioppolo F, Flamini S, Spacca G and Santilli V: Extracorporeal shock-wave therapy compared with surgery for hypertrophic long-bone nonunions. J Bone Joint Surg Am 91: 2589-2597, 2009.
15. Willems A, van der Jagt OP and Meuffels DE: Extracorporeal shock wave treatment for delayed union and nonunion fractures: A systematic review. J Orthop Trauma 33: 97-103, 2019.
16. Wu GB: Effect of extracorporeal shock wave therapy on fracture nonunion and delayed union. Med Equip 34: 99-100, 2021 (In Chinese).
17. Alkhawashki HM: Shock wave therapy of fracture nonunion. Injury 46: 2248-2252, 2015.
18. Kaulesar Sukul DM, Johannes EJ, Pierik EG, van Eijck GJ and Kristelijn MJ: The effect of high energy shock waves focused on cortical bone: An in vitro study. J Surg Res 54: 46-51, 1993.
19. Gadomski BC, McGilvray KC, Easley JT, Palmer RH, Jiao J, Li X, Qin YX and Puttlitz CM: An investigation of shock wave therapy and low-intensity pulsed ultrasound on fracture healing under reduced loading conditions in an ovine model. J Orthop Res 36: 921-929, 2018.
20. Stojadinovic A, Elster EA, Anam K, Tadaki D, Amare M, Zins S and Davis TA: Angiogenic response to extracorporeal shock wave treatment in murine skin isografts. Angiogenesis 11: 369-380, 2008.

21. Ko NY, Chang CN, Cheng CH, Yu HK and Hu GC: Comparative effectiveness of focused extracorporeal versus radial extracorporeal shockwave therapy for knee osteoarthritis-randomized controlled study. Int J Environ Res Public Health 19: 9001, 2022.
22. Sah V, Kaplan S, Ozkan S, Adanas C and Toprak M: Comparison between radial and focused types of extracorporeal shock-wave therapy in plantar calcaneal spur: A randomized sham-controlled trial. Phys Sportsmed 51: 82-87, 2023.
23. Saglam G, Cetinkaya Alisar D and Ozen S: Physical therapy versus radial extracorporeal shock wave therapy in the treatment of carpal tunnel syndrome: A randomized-controlled study. Turk J Phys Med Rehabil 68: 126-135, 2022.
24. Kertzman P, Csaszar NBM, Furia JP and Schmitz C: Radial extracorporeal shock wave therapy is efficient and safe in the treatment of fracture nonunions of superficial bones: A retrospective case series. J Orthop Surg Res 12: 164, 2017.
25. Yue L, Chen H, Feng TH, Wang R and Sun HL: Low-intensity extracorporeal shock wave therapy for midshaft clavicular delayed union: A case report and review of literature. World J Clin Cases 9: 8242-8248, 2021.
26. Wang CJ, Huang KE, Sun YC, Yang YJ, Ko JY, Weng LH and Wang FS: VEGF modulates angiogenesis and osteogenesis in shockwave-promoted fracture healing in rabbits. J Surg Res 171: 114-119, 2011.
27. Ginini JG, Emodi O, Sabo E, Maor G, Shilo D and Rachmiel A: Effects of timing of extracorporeal shock wave therapy on mandibular distraction osteogenesis: An experimental study in a rat model. J Oral Maxillofac Surg 77: 629-638, 2019.
28. Lu CC, Chou SH, Shen PC, Chou PH, Ho ML and Tien YC: Extracorporeal shock wave promotes activation of anterior cruciate ligament remnant cells and their paracrine regulation of bone marrow stromal cells' proliferation, migration, collagen synthesis, and differentiation. Bone Joint Res 9: 458-468, 2020.
29. Li B, Wang R, Huang X, Ou Y, Jia Z, Lin S, Zhang Y, Xia H and Chen B: Extracorporeal shock wave therapy promotes osteogenic differentiation in a rabbit osteoporosis model. Front Endocrinol (Lausanne) 12: 627718, 2021.
30. Song WP, Ma XH, Sun YX, Zhang L, Yao Y, Hao XY and Zeng JY: Extracorporeal shock wave therapy (ESWT) may be helpful in the osseointegration of dental implants: A hypothesis. Med Hypotheses 145: 110294, 2020.
31. Kobayashi M, Chijimatsu R, Yoshikawa H and Yoshida K: Extracorporeal shock wave therapy accelerates endochondral ossification and fracture healing in a rat femur delayed-union model. Biochem Biophys Res Commun 530: 632-637, 2020.
32. Inoue S, Hatakeyama J, Aoki H, Kuroki H, Niikura T, Oe K, Fukui T, Kuroda R, Akisue T and Moriyama H: Utilization of Mechanical stress to treat osteoporosis: The effects of electrical stimulation, radial extracorporeal shock wave, and ultrasound on experimental osteoporosis in ovariectomized rats. Calcif Tissue Int 109: 215-229, 2021.
33. Hu CC, Chang CH, Hsiao YM, Chang Y, Wu YY, Ueng SWN and Chen MF: Lipoteichoic acid accelerates bone healing by enhancing osteoblast differentiation and inhibiting osteoclast activation in a mouse model of femoral defects. Int J Mol Sci 21: 5550, 2020.
34. Wallimann A, Magrath W, Pugliese B, Stocker N, Westermann P, Heider A, Gehweiler D, Zeiter S, Claesson MJ, Richards RG, *et al*: Butyrate inhibits osteoclast activity in vitro and regulates systemic inflammation and bone healing in a murine osteotomy model compared to antibiotic-treated mice. Mediators Inflamm 2021: 8817421, 2021.
35. Li X, Wang L, Huang B, Gu Y, Luo Y, Zhi X, Hu Y, Zhang H, Gu Z, Cui J, *et al*: Targeting actin-bundling protein L-plastin as an anabolic therapy for bone loss. Sci Adv 6: eabb7135, 2020.
36. Chen Q, Xia C, Shi B, Chen C, Yang C, Mao G and Shi F: Extracorporeal shock wave combined with teriparatide-loaded hydrogel injection promotes segmental bone defects healing in osteoporosis. Tissue Eng Regen Med 18: 1021-1033, 2021.
37. Alshihri A, Niu W, Kammerer PW, Al-Askar M, Yamashita A, Kurisawa M and Spector M: The effects of shock wave stimulation of mesenchymal stem cells on proliferation, migration, and differentiation in an injectable gelatin matrix for osteogenic regeneration. J Tissue Eng Regen Med 14: 1630-1640, 2020.
38. Chen Y, Xu J, Huang Z, Yu M, Zhang Y, Chen H, Ma Z, Liao H and Hu J: An innovative approach for enhancing bone defect healing using PLGA scaffolds seeded with extracorporeal-shock-wave-treated bone marrow mesenchymal stem cells (BMSCs). Sci Rep 7: 44130, 2017.
39. Yang YQ, Tan YY, Wong R, Wenden A, Zhang LK and Rabie AB: The role of vascular endothelial growth factor in ossification. Int J Oral Sci 4: 64-68, 2012.
40. Street J, Bao M, deGuzman L, Bunting S, Peale FV Jr, Ferrara N, Steinmetz H, Hoeffel J, Cleland JL, Daugherty A, *et al*: Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover. Proc Natl Acad Sci USA 99: 9656-9661, 2002.
41. Sung PH, Yin TC, Chai HT, Chiang JY, Chen CH, Huang CR and Yip HK: Extracorporeal shock wave therapy salvages critical limb ischemia in B6 mice through upregulating cell proliferation signaling and angiogenesis. Biomedicines 10: 117, 2022.
42. Sorg H, Zwetzich I, Tilkorn DJ, Kolbenschlag J, Hauser J, Goertz O, Spindler N, Langer S and Ring A: Effects of extracorporeal shock waves on microcirculation and angiogenesis in the in vivo wound model of the diver box. Eur Surg Res 62: 134-143, 2021.
43. Modena DAO, Soares CD, Candido EC, Chaim FDM, Cazzo E and Chaim EA: Effect of extracorporeal shock waves on inflammation and angiogenesis of integumentary tissue in obese individuals: Stimulating repair and regeneration. Lasers Med Sci 37: 1289-1297, 2022.
44. Sternecker K, Geist J, Beggel S, Dietz-Laursonn K, de la Fuente M, Frank HG, Furia JP, Milz S and Schmitz C: Exposure of zebra mussels to extracorporeal shock waves demonstrates formation of new mineralized tissue inside and outside the focus zone. Biol Open 7: bio033258, 2018.
45. Wu W, Maffulli N, Furia JP, Meindlhumer L, Sternecker K, Milz S and Schmitz C: Exposure of zebra mussels to radial extracorporeal shock waves: Implications for treatment of fracture nonunions. J Orthop Surg Res 16: 707, 2021.
46. Hsu PC, Chang KV, Chiu YH, Wu WT and Ozcakar L: Comparative effectiveness of botulinum toxin injections and extracorporeal shockwave therapy for post-stroke spasticity: A systematic review and network meta-analysis. EClinicalMedicine 43: 101222, 2021.
47. Hsiao MY, Hung CY, Chang KV, Chien KL, Tu YK and Wang TG: Comparative effectiveness of autologous blood-derived products, shock-wave therapy and corticosteroids for treatment of plantar fasciitis: A network meta-analysis. Rheumatology (Oxford) 54: 1735-1743, 2015.
48. Chang KV, Chen SY, Chen WS, Tu YK and Chien KL: Comparative effectiveness of focused shock wave therapy of different intensity levels and radial shock wave therapy for treating plantar fasciitis: A systematic review and network meta-analysis. Arch Phys Med Rehabil 93: 1259-1268, 2012.
49. Gao J, Rubin JM, Chen J and O'Dell M: Ultrasound elastography to assess botulinum toxin a treatment for post-stroke spasticity: A feasibility study. Ultrasound Med Biol 45: 1094-1102, 2019.
50. Venkatakrishnan A, Francisco GE and Contreras-Vidal JL: Applications of brain-machine interface systems in stroke recovery and rehabilitation. Curr Phys Med Rehabil Rep 2: 93-105, 2014.
51. Rompe JD, Rosendahl T, Schollner C and Theis C: High-energy extracorporeal shock wave treatment of nonunions. Clin Orthop Relat Res (387) 102-111, 2001.
52. Elster EA, Stojadinovic A, Forsberg J, Shawen S, Andersen RC and Schaden W: Extracorporeal shock wave therapy for nonunion of the tibia. J Orthop Trauma 24: 133-141, 2010.
53. Zhang LH, Man LB, Huang GL and Xu X: Effect of different dosage of radial extracorporeal shock waves on fracture disunite and bone nonunions. Chinese Journal of Rehabilitation Theory and Practice 19: 978-980, 2013 (In Chinese).
54. Huang XW, Han W, Liu YJ, Zhang LH, Gong MQ and Jiang XY: Comparison of the treatment results of hypertrophic nonunion by using extracorporeal shock wave therapy(ESWT) or traditional iliac autograft and internal fixation. J Nanjing Med Univ (Natural Sciences) 35: 1432-1436, 2015 (In Chinese).
55. Wang WZ, Xing GY and Zhai L: Clinical study of extracorporeal shock wave therapy with autograf t of bone marrow for bone nonunion. Chin J Prim Med Pharm 13: 1057-1059, 2006 (In Chinese).
56. Jin X, Tan YH, Zhang ZY, Ju CJ, Yan W and Jiang HJ: A clinical study of injection of autologous cell growth factors combined with extracorporeal shock wave therapy for treatment of nonunion of lower limb fractures. J Trad Chin Orthop Trauma 30: 10-13, 2018 (In Chinese).

57. Gvozdenovic R, Presman B, Larsen MB, Radev DI, Joerring S and Jensen CH: Can CT-scan measurements of humpback deformity, dislocation, and the size of bony cysts predict union after surgery for scaphoid nonunion? J Wrist Surg 10: 418-429, 2021.
58. Doll J, Waizenegger S, Schmidmaier G, Weber MA and Fischer C: Contrast-Enhanced Ultrasound: A viable diagnostic tool in predicting treatment failure after non-union revision surgery for Upper- and Lower-limb Non-unions. Ultrasound Med Biol 47: 3147-3158, 2021.
59. Konda SR, Carlock KD, Hildebrandt KR and Egol KA: Predicting functional outcomes following fracture nonunion repair-development and validation of a risk profiling tool. J Orthop Trauma 34: e214-e220, 2020.
60. Yin J, Zhu H, Gao Y and Zhang C: Vascularized fibular grafting in treatment of femoral neck nonunion: A prognostic study based on long-term outcomes. J Bone Joint Surg Am 101: 1294-1300, 2019.
61. Christiano AV, Goch AM, Leucht P, Konda SR and Egol KA: Radiographic union score for tibia fractures predicts success with operative treatment of tibial nonunion. J Clin Orthop Trauma 10: 650-654, 2019.
62. Stojadinovic A, Kyle Potter B, Eberhardt J, Shawen SB, Andersen RC, Forsberg JA, Shwery C, Ester EA and Schaden W: Development of a prognostic naive bayesian classifier for successful treatment of nonunions. J Bone Joint Surg Am 93: 187-194, 2011.
63. Chen S, Chen X, Geng Z and Su J: The horizon of bone organoid: A perspective on construction and application. Bioact Mater 18: 15-25, 2022.
64. Xue X, Hu Y, Wang S, Chen X, Jiang Y and Su J: Fabrication of physical and chemical crosslinked hydrogels for bone tissue engineering. Bioact Mater 12: 327-339, 2021.
65. Sun C, Kang J, Yang C, Zheng J, Su Y, Dong E, Liu Y, Yao S, Shi C, Pang H, *et al*: Additive manufactured polyether-ether-ketone implants for orthopaedic applications: A narrative review. Biomater Transl 3: 116-133, 2022.
66. Li H, Yang P, Hwang J, Pageni P, Decho AW and Tang C: Antifouling and antimicrobial cobaltocenium-containing metallopolymer double-network hydrogels. Biomater Transl 3: 162-171, 2022.