Low intensity pulsed ultrasound (LIPUS) therapy has demonstrated clinical effectiveness in achieving union in a variety of fracture situations.

Few studies have investigated the effectiveness of LIPUS therapy in foot and ankle surgery.

The overall rate of union in all published studies relating to the use of LIPUS in a variety of foot and ankle fracture and fusion situations is 95%.

Some studies suggest lower healing rates (~67%) when LIPUS therapy is used to treat hindfoot fusion nonunion.

A well-powered, high-quality, randomized controlled trial is needed to demonstrate the clinical and cost effectiveness of LIPUS therapy in foot and ankle surgery.

**Keywords:** ankle; delayed union; foot; LIPUS; low intensity; nonunion; ultrasound

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**Introduction**

Fractures in the foot and ankle can occasionally pose a challenge regarding union. Fusions involving joints of the foot or ankle can similarly prove difficult to achieve sound union. Whilst there may be clearly identifiable risk factors for delayed or nonunion, it can still occur in healthy patients.\(^1,2\) There is some dissonance regarding the definition of bony union.\(^3,4\) Most studies describe clinical and/or radiological union, using a reference time point since injury or surgery. Clinical union is commonly defined as lack of pain on palpation and weight-bearing. Radiological union is frequently defined radiographically as three of four cortices in continuity in orthogonal projections. Variations exist between studies. In most foot and ankle fractures, osteotomies, and fusions, delayed union is defined as >3 months since injury/operation and nonunion is >9 months since injury/operation. ‘Normal’ time to union varies in foot and ankle fractures and radiographic union may lag behind clinical union in some cases.\(^5\) One method that has been used to achieve union of fractures, osteotomies and fusion, is the application of low intensity pulsed ultrasound (LIPUS) therapy (Table 1).\(^6\) The increasing use of LIPUS in various orthopaedic applications has included the field of foot and ankle surgery. LIPUS use in this area is becoming more popular, largely due to early promising results (Table 2).\(^7,8\) This review article will describe LIPUS treatment, the basic science that underpins its mechanism of action, and review the published literature relating to its application in foot and ankle surgery. To date, few studies have evaluated the clinical effectiveness of LIPUS therapy specifically in foot and ankle surgery. The aim of this article was to review the clinical studies reporting the outcome of union in foot and ankle surgery. Recommendations for clinicians considering LIPUS therapy in foot and ankle surgery will be provided based on the published peer-reviewed clinical evidence.

| Table 1. Indications and precautions for EXOGEN® |
|-----------------------------------------------|
| **Indications** | **Precautions** |
| Treatment of delayed unions | Skeletally immature individuals |
| Treatment of nonunions | Nonunions of the vertebrae and the skull |
| Treatment of stress fractures | Osseous defects of the vertebra and the skull |
| Accelerating repair following osteotomy | Pregnant or breast-feeding women |
| Accelerating repair in bone transport procedures | Pathological fractures due to bone pathology or malignancy |
| Accelerating repair in distraction osteogenesis procedures | |
| Treatment of joint fusion | |

Source: Taken from Bioventus EXOGEN® Ultrasound Bone Healing System Instruction Manual.
Basic science of LIPUS

Low intensity pulsed ultrasound was first applied to fracture repair in 1983.9 FDA approval was granted in 1994.10 The technology utilizes an unfocussed transducer to deliver ultrasound waves with 30 mW/cm² SATA (spatial average-temporal average) intensity, at a frequency of 1.5 MHz, pulsed at 1 KHz, over a 3.88 cm² area.10 The transducer is connected to the main operating unit and is attached to the patient with a separate fixture strap overlying their nonunion or delayed union site. Coupling gel is applied to the transducer head to aid conduction of ultrasound. The patient self-administers one daily 20-minute session until union is achieved. Its mechanism of action has been studied extensively and our understanding of this technology is constantly growing. Cell culture and in vivo experiments have revealed some key insights. LIPUS has been shown to generate nano-motion at the fracture/osteotomy site.11 This in turn triggers a series of events, via integrins on the surface of cells, acting as mechanoreceptors. Integrins act as mechanoreceptors on the surface of cells. The activation of the focal adhesion kinase (FAK) – extracellular signal-regulated kinases (ERK) pathway has been implicated. Downstream effects relate to the production of COX2 protein in cell culture models. In vivo animal models have added credence to this mechanism of action, demonstrating loss of the beneficial effect of LIPUS in COX2 knockout mice. Production of COX2 induced by LIPUS drives increased PGE₂ production, which has been shown to stimulate osteoclasts and osteoblasts. LIPUS activates cellular pathways involved in angiogenesis and generates factors important to endochondral ossification, enhancing this phase of healing (Fig. 1).10

Clinical applications of LIPUS

LIPUS therapy has been shown in a number of studies to be beneficial in achieving union in a variety of settings (Table 3).6 Leighton et al conducted a systematic review and meta-analysis of LIPUS treatment used to treat confirmed fracture nonunions.6 In this systematic review, 1441 nonunions across 13 studies were reported. None of the included studies investigated foot and ankle fractures in isolation. The pooled treatment effect size for healing from 10 studies (three were excluded as they enrolled patients whose treatment started < 90 days from injury) was 82% (95% CI: 77–87%). For established nonunions, the pooled treatment effect size for healing was 84% (95% CI: 77–91.6%). Subgroup analysis revealed hypertrophic nonunions were

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Table 2. Claimed benefits of LIPUS for bony nonunion or delayed healing

| Benefit                                                                 | Source |
|------------------------------------------------------------------------|--------|
| Reduced healing time compared with surgery                             |        |
| Avoidance of surgery and achievement of comparable clinical outcomes   |        |
| Quicker return to weight-bearing and normal daily living compared with surgery |        |
| Improved treatment accessibility with a therapy that can be self-administered |        |
| in a home environment                                                   |        |
| Reduced need for high-cost surgical intervention                       |        |
| Reduced cost because of a reduction in outpatient care, quicker recovery and return to work and normal living |        |

Note. LIPUS, low intensity pulsed ultrasound.

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Fig. 1 Summary of the basic science of key steps in LIPUS mechanism of action.
Source: Adapted from Harrison et al9 with permission.
LIPUS IN THE FOOT AND ANKLE

Table 3. Summary of published studies reporting fusion rates in foot and ankle surgery

| Author         | Journal               | Year | Study design | Patient cohort | n = | LIPUS protocol | Device | Healing rate | Healing time (mean, SD) | Data from manufacturer’s registry? | Factors influencing healing |
|----------------|-----------------------|------|--------------|----------------|-----|----------------|--------|--------------|------------------------|------------------------------|-------------------------------|
| Teoh et al     | The Foot              | 2018 | Case series  | 5th metatarsal  | 30  | 20-minute daily | Exogen | 27/30 (90%)  | 88 days (5.9)          | No                           | Smoking status                |
|                |                       |      |              | fracture nonunions (>3 and <9 months since injury) |     | session self-administered (up to 150 days) |        |              |                        |                              |                               |
| Mayr et al     | Arch Orthop Trauma Surg | 2000 | Case series  | Registry data of all fracture delayed (up to 9 months) and nonunions (>9 months since injury) (data on foot and ankle fractures extracted) | 149 | 20-minute daily | Exogen | 198/214 (92.5%) | 100 days (19.2)       | Yes                          | Calcium channel blockers; NSAIDs; Smoking status; Renal disease; Vascular insufficiency |
| Zura et al     | Injury                | 2015 | Case series  | Chronic (>365 days since injury) nonunions | 100 | 20-minute daily | Exogen | 86/100 (86%) | N/A                    | Yes                          | Patient age                  |
| Zura et al     | BMC Musculoskeletal Diseases | 2015 | Case series  | Acute (>90 days since injury) fractures | 555 | 20-minute daily | Exogen | 545/555 (98%) | N/A                    | Yes                          | Comorbidities (DM, vascular insufficiency, osteoporosis, cancer, RA); Smoking status; Medications (Steroids, insulin, calcium channel blockers, antibiotics, anticoagulants, NSAIDs) |
| Majeed et al   | Foot & Ankle surgery  | 2019 | Case series  | Lower leg/ankle fractures; hindfoot fusions; midfoot/forefoot fractures and fusions (>9 months since index injury/procedure) | 47  | 20-minute daily | Exogen | (41/47) 87%  | 6 months (range 3–15) | No                           | N/A                          |
| Nolte et al    | Injury                | 2016 | Cohort study | Acute, delayed union, nonunion in metatarsal fractures | 594 | 20-minute daily | Exogen | 574/595 (97%) | N/A                    | Yes                          | N/A                          |
| Jones et al    | Foot & Ankle International | 2006 | Case series  | Patients undergoing revision hindfoot fusion for nonunion | 19* | 20-minute daily | Exogen | 13/19 (68%)  | 11.8 weeks (range 6–30) | No                           | N/A                          |
| Coughlin et al | Foot & Ankle International | 2008 | Cohort study | Primary subtalar joint fusion + LIPUS vs primary subtalar joint fusion alone | 15**| 20-minute daily | Exogen | 12/15 (80%)   | N/A                    | No                           | N/A                          |
| Mirza et al    | Foot & Ankle surgery  | 2018 | Case series  | Delayed or nonunion following foot or ankle fusion | 18  | 20-minute daily | Exogen | 12/18 (67%)  | 36.5 weeks (range 24–60) | No                           | N/A                          |

*19 joints in 13 patients.
**15 patients in each group (15 received LIPUS).

Twice as likely to heal as atrophic nonunions when LIPUS was applied. Application of LIPUS within six months of the last surgical intervention yielded a more favourable result than those treated with LIPUS > 12 months since their last surgery (OR 5.72, 95% CI: 1.62, 20.22). Patient age, smoking status, and fracture age did not significantly influence the healing rate in this meta-analysis.

The National Institute for Health and Care Excellence in United Kingdom updated its guidelines on the use of the EXOGEN® (trade name for LIPUS) ultrasound bone healing system for long bone fractures with nonunion or delayed healing recently in 2019. They suggested that adopting the EXOGEN® ultrasound bone healing system to treat long bone fractures with nonunion is supported by the clinical evidence, which shows high rates of fracture healing and is associated with an estimated cost saving of £2,407 (~€2,648) per patient compared with current management, through avoiding surgery. However, for long bone fractures with delayed healing, there are substantial uncertainties about the rate at which bone healing progresses...
without adjunctive treatment between three and nine months after fracture, and about whether or not surgery would be necessary. These uncertainties result in a range of cost consequences, some cost saving and others that are more costly than current management. The model considered to be most appropriate to estimate EXOGEN® treatment in delayed union would be more costly than current management. The Committee therefore judged that the case for adoption of EXOGEN® to treat long bone fractures with delayed healing was not supported by the current evidence.

**LIPUS in foot and ankle fractures**

*In delayed union and nonunion*

LIPUS therapy has been utilized in a number of foot and ankle fracture settings (Fig. 2). Majeed et al reported a mixed series of foot and ankle (F&A) patients (both fracture and elective surgery patients) with nonunion. Overall, 37/47 (79%) of patients receiving LIPUS treatment healed in his series. However, clinical union was defined as an asymptomatic patient, which demonstrated radiological union in only 26/37 patients (70%). Of the 10 patients with persistent pain and nonunion, six underwent revision surgery.

Specific to F&A fractures in their series, the healing rate was 93% (13/14) in patients with tibial/ankle fracture nonunion and 78% (14/18) in patients with midfoot/forefoot fusions/fractures nonunion. Teoh et al presented a case series of 30 patients treated with LIPUS for ununited 5th metatarsal fractures, initially treated conservatively. Clinical and radiological union was achieved in 90%. Two-thirds of those that failed LIPUS treatment were symptomatic and required surgery (one ORIF, one excision of Type 1 fracture fragment). All three failures occurred in smokers; however, given that the numbers were small, it is unclear whether this observation is relevant. Mayr et al also noted that those who failed to heal their delayed or nonunion after LIPUS treatment were more likely to be smokers. Extracting data in their registry series specific to foot and ankle only (214/1317), foot fracture nonunions (excluding metatarsal fractures) had a 90% (18/20) healing rate with LIPUS treatment at an average of 138 days (SD 18.1) and metatarsal fracture nonunions had a 78% (14/18) healing rate (mean 117 days, SD 17.0). In their delayed unions group, the union rates following LIPUS treatment are as follows: foot, 91% (10/11); metatarsal, 96% (81/84); calcaneus, 89% (8/9); navicular 83% (5/6); ankle, 92% (36/39); fibula, 96% (26/27). This gives a healing rate of 94% for delayed union and 84% for nonunion. Based on these findings, it is reasonable to consider a trial of LIPUS therapy in delayed union or established nonunion foot and ankle fractures, especially in patients wishing to avoid surgical intervention.

*Acute fractures*

One potential utility of LIPUS is in acute foot and ankle fractures, especially in certain high-risk groups, to increase the chances of union. Utilizing a large post-market surveillance registry database, Zura et al reported an overall healing rate for all fractures sustained < 90 days prior to LIPUS treatment as 96% (4032/4190). However, this cohort excluded patients lost to follow-up and deemed non-compliant with treatment (1575 patients). The authors reported higher union rates for foot and ankle fractures compared to the overall average rate of healing for all fractures. In this study, 122/125 (98%) ankle fractures and 423/430 (98%) metatarsal fractures healed with LIPUS treatment. Given most acute foot and ankle fractures will heal, often with conservative treatment alone, it is unclear the treatment effect size and the cost effectiveness of adjunctive LIPUS therapy in this group.

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*Fig. 2* Radiographs of a healthy 74-year-old with a stable Weber B distal fibula fracture. (A) Initial anteroposterior (AP) radiograph; (B) radiograph taken 212 days after injury showing painful nonunion confirmed with magnetic resonance imaging (not shown); (C) fluoroscopic guided targeting of placement of transducer for accurate localization of EXOGEN® therapy; (D) AP radiograph demonstrating radiographic union after 79 doses of EXOGEN® with 100% compliance.
Acute vs. delayed union or nonunion

Nolte et al compared registry data on patients with all metatarsal fractures, acute and those with delayed or non-union, receiving LIPUS treatment compared with ‘standard care’ using propensity matching from a health claims database (Truven Health Analytics). They found no difference in healing between the cohorts (LIPUS 578/594 97.3% vs. standard care 566/594 95.3%, p = 0.065). In this analysis, the LIPUS cohort included those receiving LIPUS as a standalone intervention and those who received surgery with LIPUS therapy as an adjunct. When investigating those receiving LIPUS treatment as a standalone treatment, without concomitant surgery, vs. standard care (Truven cohort), they found 521/535 (97.4%) healed with LIPUS treatment compared to 504/535 (94.2%) (p = 0.0097). The Truven cohort had significantly more obese and morbidly obese patients than the LIPUS cohort (p = 0.0099), which may have influenced the outcome. It is also unclear what proportion of the Truven cohort received surgical intervention, which is an additional confounder. The absolute risk reduction in treating metatarsal fractures with LIPUS vs. standard care is 0.027, resulting in a need to treat number of 36.8 patients. Subgroup analysis, after propensity matching, demonstrated improved healing when comparing LIPUS treatment with standard care for acute (< 90 days since injury) fractures (361/368 98.1% vs. 351/368 95.4%, p = 0.0381). Surprisingly, they found no improvement in healing rate for delayed or non-unions in metatarsal fractures between the two cohorts (LIPUS 217/226 96.0% vs. 212/226 93.8%, p = 0.2851).

Chronic nonunions (defined as lack of clinical or radiological union > 365 days since injury)

The ability of LIPUS to achieve union in extreme nonunion cases, precluding the need for surgery, is desirable. LIPUS has been in evaluated in such chronic cases. In a study of chronic nonunions, defined as lack of clinical or radiological union > 365 days since injury, Zura et al demonstrated healing in 661/767 (86%) when LIPUS treatment was used as a standalone intervention, or at least 90 days after the last surgical procedure. The heal rate for his nonunion series, specific to the foot and ankle, was similar to his overall success rate: ankle, 35/41, 85.4%; metatarsal, 31/36, 86.1%; foot, 20/23, 87.0%.

Most studies reporting the outcome of LIPUS therapy in foot and ankle fractures are level 3 or 4 evidence. There is significant heterogeneity in the cohorts described in these studies. Firstly, studies have investigated the use of LIPUS in a wide range of foot and ankle pathology, from acute fractures to established chronic unions. Secondly, some studies included both elective fusion and fracture nonunions. Thirdly, studies have reported data from a large registry, with foot and ankle cases forming part of a subgroup analysis. Fourthly, LIPUS therapy has been studied as a standalone intervention, whilst others report its use as an adjunct to primary or revision surgery.

Application in foot and ankle fusion

Failed fusion

Surgeons have employed LIPUS therapy to achieve union following failed foot and ankle fusion. This can be done as an independent intervention following nonunion after fusion (Fig. 3), or in conjunction with revision surgery. In the context of established delayed or nonunion following fusion in the foot or ankle, Mirza et al applied LIPUS therapy in 18 patients. They reported 12/18 patients achieved union with LIPUS therapy alone at a mean of 4.8 months (range 3–6 months). Of the six failures, three opted for revision surgery, and one had an amputation. They reported that small joint fusions (one naviculocuneiform; one talonavicuclar; and eight first metatarsophalangeal joints) healed with LIPUS therapy in 9/10 patients. The authors suggest that LIPUS therapy may be less effective in the tibial joint or hindfoot fusions. Similarly, Majeed et al reported only 10/15 (67%) hindfoot fusion nonunions achieved union with LIPUS therapy. They attributed the poorer healing rates in the hindfoot fusion group to the increased distance between the transducer and the fusion site, and greater volume of adipose tissue in this area. Contrary to the lower rates of union reported by these two studies, Mayr et al reported higher healing amongst ankle fusion using LIPUS therapy (union rate 18/22, 82%).

As an adjunct post-fusion surgery

The use of adjunct LIPUS treatment in revision hindfoot fusion was reported in a case series of 19 fusions in 13 patients. Using CT scans postoperatively, they applied a novel grading system to account for metal artefacts, and reported union as nonunion (0–33% joint surface fused), partial union (33–66% joint surface fused), or solid union (66–100% joint surface fused). One out of 19 joints had a nonunion, which occurred in an isolated revision subtalar fusion; 5/19 had a partial union; 13/19 had a solid union. Given no control group was used in this study, it is unclear what proportion of these patients would have united their revision fusion. Coughlin et al reported the use of adjunct LIPUS treatment for subtalar joint fusions compared to surgery alone. They compared the radiological and clinical outcomes of 15 patients receiving LIPUS after surgery with a control group of 15 patients receiving surgery alone. LIPUS was applied using a medial window within the post-operative cast for 12 weeks post-surgery. CT scans were obtained at serial time points. They consistently demonstrated larger surface area of fusion of the posterior facet area in the LIPUS group compared to the control group from 6 weeks to 12 months post surgery. The rate of healing showed a statistically significant difference with
the LIPUS group when compared to the control (no LIPUS) group only at 12 weeks for CT (p = 0.017), and only at nine weeks on plain radiographs (p = 0.034). This was not statistically significant at all other time points (6, 9, 24, and 52 weeks). Therefore, the true clinical significance of this is debatable. It is likely a reflection of low numbers in this study and the difficulties in accurately assessing fusion on CT scans due to implant artefacts.

Pooling the data from all studies pertaining to foot and ankle fractures and fusions demonstrates a high rate of union (95%, SD 11.5) (Fig. 4). It is difficult to know, with any certainty, the clinical and cost effectiveness of LIPUS used in this patient group. A well-powered randomized controlled trial with an appropriate control group, ideally a placebo-control, is required to determine this.

Fig. 3 Healthy 54-year-old underwent elective left 1st metatarsophalangeal joint (MTPJ) fusion. (A) Weight-bearing anteroposterior (AP) left-foot radiograph taken 101 days post surgery demonstrating painful delayed union. (B) Weight-bearing oblique view left-foot radiograph taken 101 days post surgery, demonstrating painful nonunion. (C) Weight-bearing AP left-foot radiograph demonstrating radiographic union (clinically asymptomatic) after 98 doses of EXOGEN® with 98% compliance. (D) Weight-bearing lateral left-foot radiograph demonstrating radiographic union (clinically asymptomatic) after 98 doses of EXOGEN® with 98% compliance.

Fig. 4 Rate of union in studies investigating use of LIPUS therapy in the foot and ankle.
Future research

Despite early promising results, further research investigating the efficacy, effectiveness, and optimal indications for LIPUS therapy in the foot and ankle is needed. Some research questions may require randomized controlled trials (RCTs), whilst others may be best investigated using a large prospective data registry. Key questions relating to the clinical efficacy and clinical effectiveness of LIPUS therapy in the foot and ankle exist. A clinical efficacy study investigating the use of LIPUS therapy in a particular area, such as delayed unions in 5th metatarsal fractures, may utilize a double-blinded, randomized, sham machine, placebo-controlled trial. A clinical effectiveness study, investigating LIPUS use in the area of the foot and ankle, for example, may take the form of a pragmatic RCT, with the LIPUS treatment group including a wider range of conditions. The control group may involve ‘standard care’. For other research questions, large prospective cohorts, such as studies utilizing the Exogen registry, can help increase the numbers included for analysis. The application of LIPUS in hindfoot arthrosis nonunion cases is still a relatively small area. The observation of lower healing rates in hindfoot fusion nonunions treated with LIPUS can be further investigated using registry data. These studies have a higher risk of bias and caution must be used when interpreting their results. A control group, propensity matched for significant demographic factors, should be included to allow meaningful comparison (e.g. use of LIPUS therapy in midfoot vs hindfoot fusion nonunions).

There are many challenges to conducting such research. Several confounders can be accounted for, whilst others may not. Randomization sequences may include stratification for certain factors, to reduce the risk they may impact the primary outcome. Such factors may include obesity, comorbidities, smoking status, and steroid use. Any pragmatic study allowing broad inclusion criteria may choose to stratify for number of hindfoot fusions, to limit their potentially lower healing rate from influencing the overall primary outcome. Studies involving registry data may yield significant statistical results that demonstrate correlation, yet causation may remain unclear. Additionally, there may be heterogeneity between delayed union and nonunion definitions. Similarly, for defining union, it may not be practical, nor ethical, to demonstrate radiographic union in all cases. This is particularly the case in an asymptomatic hindfoot fusion where radiographs are inconclusive and CT may be required to demonstrate union definitively. Some studies may prove difficult to enrol patients. Established nonunions are painful and represent a significant burden to the patient. Patients may not wish to be enrolled into a study utilizing a LIPUS treatment regime spanning 3–6 months, when the alternative may be revision surgery, yielding potentially a quicker recovery. Ultimately, these studies will require clinical equipoise, both in the patient and their treating surgeon.

Conclusions

LIPUS therapy has an established scientific basis in fracture repair. The mechanism of action is thought to be from nano-motion at the repair site resulting in COX2 production through integrins and local adhesion kinases. Resultant PGE2 production stimulates osteoclasts. Coupled with increased angiogenesis, LIPUS has been shown to enhance the endochondral ossification phase of fracture repair.

Clinicians may consider using LIPUS therapy in high-risk patients for nonunion in acute fractures. Delayed or nonunion of foot and ankle fractures, especially of the 5th metatarsal, may yield good rates of union with LIPUS therapy as a standalone or adjunct to surgical intervention.

There is limited evidence to support the use of LIPUS therapy for improving fusion rates in foot and ankle fusions. Some studies suggest lower rates of union in hindfoot fusions specifically.

Studies to date have been limited by risk of bias due to methodological design. High-quality, low risk of bias, multicentre, placebo-controlled RCTs are needed to demonstrate clinical effectiveness for utilizing LIPUS in foot and ankle fractures and fusions to achieve sound union.
REFERENCES

1. Thevendran G, Younger A, Pinney S. Current concepts review: risk factors for nonunions in foot and ankle arthrodeses. Foot Ankle Int 2012;33:1031–1040.
2. Thevendran G, Shah K, Pinney SJ, Younger AS. Perceived risk factors for nonunion following foot and ankle arthrodesis. J Orthop Surg (Hong Kong) 2017;25:230949001770203.
3. Morshed S, Corrales L, Genant H, Miclau T III. Outcome assessment in clinical trials of fracture-healing. J Bone Joint Surg Am 2008;90:62–67.
4. Bhandari M, Fong K, Sprague S, Williams D, Petrisor B. Variability in the definition and perceived causes of delayed unions and nonunions: a cross-sectional, multinational survey of orthopaedic surgeons. J Bone Joint Surg Am 2012;94:e1091–e1096.
5. Griffin XL, Parsons N, Costa ML, Metcalfe D. Ultrasound and shockwave therapy for acute fractures in adults. Cochrane Database Syst Rev 2014;6:CD008579.
6. Leighton R, Watson JT, Giannoudis P, Papakostidis C, Harrison A, Steen RG. Healing of fracture nonunions treated with low-intensity pulsed ultrasound (LIPOS): a systematic review and meta-analysis. Injury 2017;48:1339–1347.
7. Teoh KH, Whitham R, Wong JF, Hariharan K. The use of low-intensity pulsed ultrasound in treating delayed union of fifth metatarsal fractures. Foot (Edinb) 2018;35:52–55.
8. Majeed H, Karim T, Davenport J, et al. Clinical and patient-reported outcomes following Low Intensity Pulsed Ultrasound (LIPOS, Exogen) for established post-traumatic and post-surgical nonunion in the foot and ankle. Foot Ankle Surg 2020;26:405–411.
9. Duarte LR. The stimulation of bone growth by ultrasound. Arch Orthop Trauma Surg 1983;101:153–159.
10. Harrison A, Lin S, Pounder N, Mikuni-Takagaki Y. Mode and mechanism of low intensity pulsed ultrasound (LIPOS) in fracture repair. Ultrasound 2016;70:45–52.
11. Greenleaf JF, Kinnick R, Bolander M. Ultrasonically induced motion in tissue during fracture treatment? Ultrasound Med Biol 2003;29:5157–5158.
12. Mayr E, Frankel V, Rüter A. Ultrasound: an alternative healing method for nonunions? Arch Orthop Trauma Surg 2000;120:1–8.
13. Zura R, Mehta S, Della Rocca GJ, Jones J, Steen RG. A cohort study of 4,190 patients treated with low-intensity pulsed ultrasound (LIPOS): findings in the elderly versus all patients. BMC Musculoskelet Disord 2015;16:45.
14. Nolte P, Anderson R, Strauss E, et al. Heal rate of metatarsal fractures: a propensity-matching study of patients treated with low-intensity pulsed ultrasound (LIPOS) vs. surgical and other treatments. Injury 2016;47:2584–2590.
15. Zura R, Della Rocca GJ, Mehta S, et al. Treatment of chronic (> 1 year) fracture nonunion: heal rate in a cohort of 767 patients treated with low-intensity pulsed ultrasound (LIPOS). Injury 2015;46:2036–2041.
16. Mirza YH, Teoh KH, Golding D, Wong JF, NathdwaraWala Y. Is there a role for low intensity pulsed ultrasound (LIPOS) in delayed or nonunion following arthrodesis in foot and ankle surgery? Foot Ankle Surg 2019;25:842–848.
17. Jones CP, Coughlin MJ, Shurnas PS. Prospective CT scan evaluation of hindfoot nonunions treated with revision surgery and low-intensity ultrasound stimulation. Foot Ankle Int 2006;27:229–235.
18. Coughlin MJ, Smith BW, Traugber P. The evaluation of the healing rate of subtalar arthrodeses, part 2: the effect of low-intensity ultrasound stimulation. Foot Ankle Int 2008;29:970–977.
19. (NICE) NIfHaCE. EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. In: (NICE) NIfHaCE, ed, 2013:1–28. https://www.nice.org.uk/guidance/mtg12/chapter/1-Recommendations (date last accessed 20 September 2020).