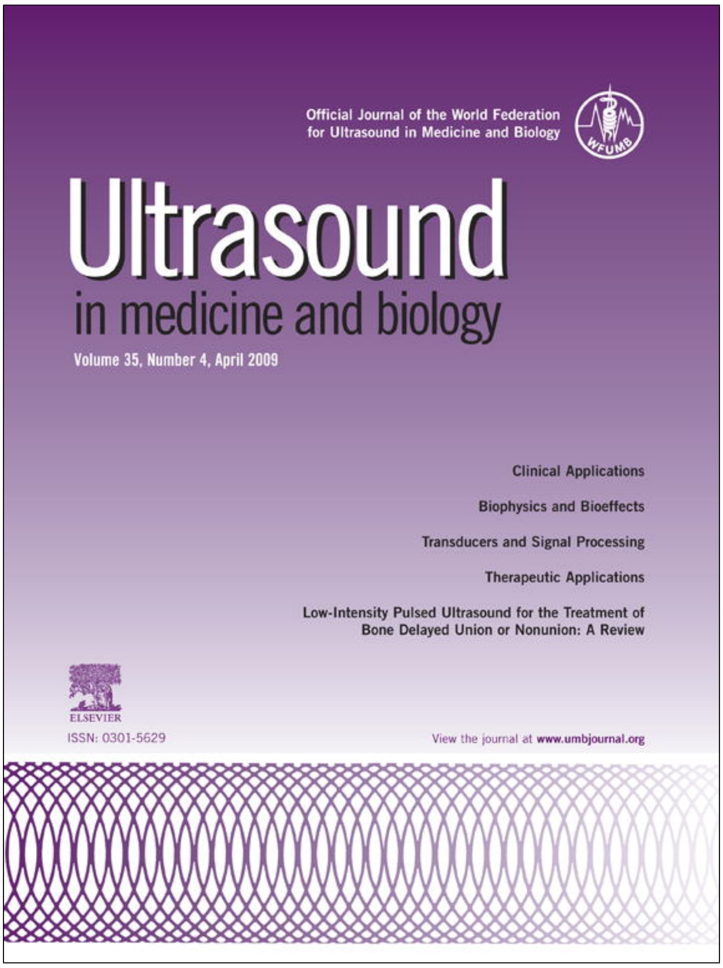

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● *Review*

LOW-INTENSITY PULSED ULTRASOUND FOR THE TREATMENT OF BONE DELAYED UNION OR NONUNION: A REVIEW

Carlo L. Romano, Delia Romano, and Nicola Logoluso
I.R.C.C.S. Istituto Ortopedico Galeazzi, Milano, Italy

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Abstract—The goal of this review is to present the most updated knowledge derived from basic science, animal studies and clinical trials, concerning biophysical stimulation of bone repair through low-intensity pulsed ultrasound (LIPUS), with particular reference to the management of delayed unions and nonunions. Low-intensity pulsed ultrasound LIPUS has been proved to significantly stimulate and accelerate fresh fracture healing in animal studies and in randomized controlled clinical trials. LIPUS also appears as an effective and safe home treatment of aseptic and septic delayed-unions and nonunions, with a healing rate ranging from 70% to 93% in different, nonrandomized, studies. Advantages of the use of this technology that may avoid the need for additional complex operations for the treatment of nonunions, include efficacy, safety, ease of use and favourable cost/benefit ratio. Outcomes depend on the site of nonunion, time elapsed from trauma, stability at the site of nonunion and host type. The detailed biophysical process by which low-intensity pulsed ultrasound LIPUS stimulates bone regeneration still remains unknown, even if various effects on bone cells *in vitro* and *in vivo* have been described. (E-mail: carlo.romano@grupposandonato.it) © 2009 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Low-intensity pulsed ultrasound, LIPUS, Fracture healing, Delayed unions, Nonunions, Callus formation.**

INTRODUCTION

Several millions of fractures occur annually worldwide, with nearly 6 million fractures reported in the United States alone (Einhorn 1995). The healing process of an injured bone requires proper reduction and fixation of the fracture site and the sequential activation of several different cell types and bioactive molecules.

Even with the most advanced treatment methods today available, approximately 5% to 10% of fractures do not heal. When the repair process is not sufficient to restore bony continuity within 3 mo from trauma or intervention, then a “delayed union” is said to occur; when bone healing does not take place after 9 mo, a “nonunion” occurs. Risk factors for delayed or nonunions include specific fracture site with poor blood supply, fracture comminution or bone gap, infection and/or extensive soft tissue damage, inadequate fracture fixation, and so on. Smoking, diabetes, alcohol abuse, old age and other systemic conditions are also important well known contributing factors to nonunions. Both delayed and nonunions lead to additional suffering and prolonged functional impairment to the patients and to increased costs for the health care systems (Heckman et al. 1997).

Nonunions may often require additional complex surgical procedures to heal (Einhorn 1995) and nonunions have also been defined as “a state in which there is the failure of a fracture to heal within the expected time and where the fracture will not heal without intervention” (Mandt et al. 1987). In fact, open surgical debridement of the nonunion site and application of internal or external fixation, in most cases with bone grafting, is still considered by many authors as the “gold standard” of nonunion treatment. The success rate of the surgical treatment of nonunions is between 70% and 90%, depending on the bone location and surgical method (Boyd et al. 1961; Healy et al. 1990; Wu et al. 1996; Ackerman et al. 1988; Cooney et al. 1980; Marsh et al. 1997).

The possibility of stimulating bone healing through physical methods has been widely investigated in the last 50 y. In nonunion cases where surgery may not be required because there is acceptable stability, alignment

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Address correspondence to: Prof. Carlo L. Romanò, I.R.C.C.S. Istituto Ortopedico Galeazzi (a), Via R. Galeazzi, 4, 20161 Milano, Italy. E-mail: carlo.romano@grupposandonato.it.

and limb length discrepancy, several biophysical treatment methods have been proposed in recent years to achieve a heal rate similar to that of surgery: pulsed electromagnetic fields (Gossling et al. 1992; Hinsenkamp et al. 1985), electrical stimulation, induced by direct current and capacitive coupling (Brighton et al. 1981, 1985; Heppenstall 1983; Scott et al. 1994), extracorporeal shock-wave therapy, usually performed as middle- or high-energy shock-wave therapy (Diesch 1997; Rompe et al. 2001; Wang et al. 2001) and low-intensity pulsed ultrasound. While experimental and clinical studies with highly significant evidence levels did show a positive effect of low-intensity pulsed ultrasound on accelerating bone healing of fresh fractures (Corradi et al. 1953; Heckman et al. 1994; Kristiansen et al. 1997) and in distraction osteogenesis (Claes et al. 2005; Sakurakichi et al. 2004; Eberson et al. 2003; Shimazaki et al. 2000), in this review, we will particularly focus on the effectiveness and safety of low-intensity pulsed ultrasound as a conservative treatment option for delayed union and nonunions (Frankel et al. 2001; Mayr et al. 2000; Gebauer et al. 2005) that still remain the most challenging application field for biophysical methods of stimulation of bone repair.

HISTORIC BACKGROUND

The first reports on the possibility to stimulate osteogenesis with ultrasound dates back to years 1949 to 1950 (Buchtala et al. 1950). In the same years, Maintz (1950) showed no histologic and radiographic changes after ultrasound treatment of rabbit radial fractures at 500 mW/cm^2, while reduced callus formation was observed at higher intensities (1000, 1500, 2500 mW/cm2). At the Gaetano Pini Orthopaedic Institute of Milan, Italy, Corradi and Cozzolino (1953) confirmed the acceleration of bone healing of fresh fractures compared with controls in rabbit radii, through ultrasound stimulation at 500 mW/cm^2 and excluded pathologic changes in the callus formation. They also reported similar results in humans, in a limited clinical series, pointing out the importance of maintaining the stability at the fracture site, the most relevant effect of ultrasound on periosteal new bone formation and proposing the stimulation through a hole in the cast. Accelerated bone healing was more recently confirmed in the studies on rabbit tibiae fractures made by Klug and coworkers (1986), while Chang et al. (2002) demonstrated a 36% increase in new bone formation and an 80% increase in torsional stiffness of limbs stimulated with 500 mW/cm^2 ultrasound compared with untreated limbs. Higher ultrasound intensities (5000 to 25,000 mW/cm2) have been reported to inhibit bone healing or induce necrosis and fibrous tissue formation in animal models (Bender et al. 1954; Herrick et al. 1956; Ardan et al. 1957). In these early studies, the ultrasound was continuous and the value of the intensity cited refers to the spatial average value.

At the beginning of the 1980s in Brazil, Duarte (1983) was the first to develop and clinically use biophysical treatment with low-intensity pulsed ultrasound system (LIPUS) to stimulate bone osteogenesis. The signal of LIPUS used by Duarte consisted of 200 ms burst of 1.5 MHz sine waves repeating at 1 kHz and delivering 30 mW/cm^2 spatial averaged and temporal averaged (SATA) intensity. In the following discussion, the term LIPUS will be used for applications of low-intensity pulsed ultrasound in which the conditions are similar to those used by Duarte (1983). Pilla et al. (1990) in a placebo controlled study of bilateral fibular osteotomies in rabbits showed that LIPUS applied for 20 min/d significantly accelerated the recovery of torsional strength and stiffness. Since then, several experimental studies have confirmed the capability of LIPUS to accelerate and increase the fracture healing process in various animal models (Wang et al. 1994; Yang et al. 1996). The use of LIPUS to accelerate bone healing in fresh fractures gradually extended to the rest of the world. In 1994, in the United States, a multicenter placebo-controlled clinical trial on closed or grade-I open tibial fractures (Heckman 1994) could demonstrate a significant (24%) reduction in the time to clinical healing, as well as a 38% decrease in the time to overall (clinical and radiographic) healing, compared with the control group. Rubin et al. (2001) reported that The Food and Drug Administration approved the use of low-intensity ultrasound for the accelerated healing of fresh fractures in October 1994 and for the treatment of established nonunions in February 2000. The clinical results were confirmed in other double-blind, randomized, placebo controlled clinical trials in wrist fractures (Kristiansen et al. 1997) and high energy tibial fractures (Leung et al. 2004).

LIPUS PARAMETERS AND TREATMENT MODALITIES

While ultrasound has been shown to improve radiographic fracture healing and increase bone density in rat femora at intensities as low as 11.8mW/cm^2, that lay in the range of those used in diagnostic setting (Heybeli et al. 2002), there is evidence that, in the range of low intensities (below 100 mW/cm^2), the response of osteoblasts to the application of ultrasound is directly related, *in vitro*, to the applied intensity (Harle et al. 2001).

The most commonly used signal frequency to stimulate osteogenesis is 1.5 MHz but higher values (3 MHz) were also proven to be effective in different animal models and at various intensities (Dyson et al. 1983; Tsai et al. 1992; Wang et al. 1994).

Table 1. Outcomes of the most relevant studies on low intensities pulsed ultrasound treatment for delayed and non unions

Authors	(Numbers of cases)	Delayed union (% healing)	Non unions (% healing)	Notes
Jingushi S. Mizuko K, Matsushita T, Iteman M (2007)	72		75	Nationwide prospective study in Japan
Romano CL, Zavatarelli A, Meani E (2006)	49		85	Septic nonunions
Gebauer D, Mayer E, Orthrer B, et Al (2005)	67		85	Average time to healing: 6 months
Rubin C, Bolander M, Ryaby JP, Hadjiargyrou M (2001)	1370	89		Data from prescription-use registry in USA
Rubin C, Bolander M, Ryaby JP, Hadjiargyrou M (2001)	1546		83	Data from prescription-use registry in USA
Nolte PA, van der Krans A, Patka P, et Al (2001)	29		86	
Mayr E, Wagner S. Ecker M, Rueter A (2002)	64	86		
Mayr E, Wagner S, Ecker M, Rueter A (2002)	36		86	
Duarte R, Xavier M, Choffle M, Mc Cabe JM (1996)	385		85	
Xavier and Duarte (1983)	26		70	

Concerning LIPUS treatment modalities, the device is applied to the skin, previously covered by a gel, corresponding to the point of fracture, for 20 min a day. The treatment is usually self-administered by the patient at home, after being properly instructed on the correct positioning of the device, for a period ranging from 2 to 6 mo or more, until healing is completed.

EXPERIMENTAL AND CLINICAL DATA

The efficacy of LIPUS to accelerate bone healing after fresh fractures has been largely described in animal models but experimental data supporting a similar effect for nonunions are scarce. In the clinical setting, nonunions appear as the result of different (and sometimes not well understood) conditions that prevented bone healing and the reasons for nonunion may vary in different patients, making it particularly difficult to establish an accepted experimental model of this complication. Using a rat model of nonunion by muscle interposition in the fractured tibia of both limbs, Takikawa et al. (2001) showed a 50% bone healing progression on radiologic examination of the bones exposed to ultrasound treatment at 6 wk, compared with no healing progression in any of the control tibias. These results were confirmed on three-dimensional X-rays and in histologic examination.

Several prospective clinical studies evaluated the efficacy of LIPUS for the treatment of delayed and nonunions in humans but ethical considerations and the difficulty of recruiting homogeneous series of patients prevents the possibility of doing double-blind, randomized, studies. In most of the available studies, each patient acts as his or her own control, the treatment with LIPUS being the only variable introduced in a patient with established delayed- or nonunion. It is worth to say that this limit also applies for all other current treatment methods of nonunions, including surgical treatments. The outcomes of most relevant published studies are reported in Table 1.

Duarte and coworkers, in the most recent of two retrospective studies, reported an 85% healing rate on 385 nonunions (Xavier et al. 1983; Duarte et al. 1996). Similar results had been reported by Mayr et al. (2002), Nolte et al. (2001) and by Gebauer et al. (2005) with an 86% healing rate in, respectively, 29 and 67 long-lasting nonunions, treated only with LIPUS. Time to healing averaged 6 mo after the initiation of daily ultrasound application.

A recently published, nationwide, prospective study for LIPUS treatment on delayed union and nonunion in Japan, analyzed the factors that influence the union rate (Jingushi et al. 2007). In this study, the mean time from the most recent operation to the beginning of LIPUS treatment was 11.5 (3 to 68) mo and the union rate was 75% in 72 cases of long bone fractures. There was a significant relationship between the union rate and the period from the most recent operation to the beginning of LIPUS treatment in all cases and a significant relationship between the union rate and the time when a radiologic improvement was first observed after the beginning of the treatment.

When LIPUS treatment was started within 6 mo of the most recent operation, 89.7% of all fractures healed. When an improvement in the radiologic changes at the fracture site was observed after 4 mo in those cases, then the sensitivity and specificity for predicting bone union were more than 90%.

We recommend starting LIPUS treatment within 6 mo from the most recent operation and "because LIPUS has been shown to be effective without causing either serious invasiveness or any undue risk to the patient, it


(a)
D
(b)
DX
(c)

may be considered the treatment of first choice for cases of postoperative delayed union or nonunion."

The healing rate is higher for delayed unions than for nonunions and results differ among various nonunion locations. Rubin et al. (2001) reported the results of prescription-use registry database as of June 2000 and found that delayed unions (151 to 255 d after the fracture) and nonunions (more than 255 d after the injury) had an overall healing rate of 89% (n = 1370) and 83% (n = 1546), respectively. When the location of nonunion was considered, data show 69% healing rate for the humerus (102 of 148), 82% for the femur (213 of 259), 84% for the tibia (404 of 483), 86% for the scaphoid (101 of 118), 87% for the radius/ulna (60 of 69) and 89% for the metatarsals (81 of 91).

When a fracture does not show radiologic signs of healing, in the presence of a local bacterial infection, a septic delayed- or nonunion is said to occur. This is one of the most challenging clinical occurrences since infection adds significant delay in bone healing and may require specific surgical treatments. LIPUS has been shown by our group to be effective even in the presence of septic nonunions (Romanò et al. 1999, 2006). Our prospective, nonrandomized study, included 49 patients affected by septic nonunions; each patient was his or her own control. LIPUS 20 min/d and antibiotic treatment were the only administered treatments. Need for further surgical intervention or persistence of nonunion at follow-up were considered failures. Patients had an average of 1.6 ± 2 previous surgical interventions.

The average time between trauma and start of ultrasound therapy ranged from 8 mo to 6 y. The average length of treatment was 126 ± 44 d (from a minimum of 90 to a maximum of 240 d).

Bone healing was achieved in 39 patients (85.1 %), seven were considered failures, while three patients decided to discontinue the treatment. There were no side effects due to LIPUS, even in presence of metallic implants and infection. Patients felt no discomfort during therapy.

Takaaki and colleagues (2005) treated with low-intensity pulsed ultrasound LIPUS a 17-year-old man with MRSA osteomyelitis of the femoral shaft after treatment for a closed fracture by an external fixator. Six weeks after radical debridement and resection at the infected site, the cement beads containing antibiotics were removed and cultures of the intraoperative specimens were negative. The defect remained with a gap of 5.0 cm in length. A small callus was observed on the medial side of the defect on a radiograph of anteroposterior view. However, the size of the defect and callus remained unchanged over a 6-wk period, so low-intensity pulsed ultrasound therapy was applied to the defect site. After 2 mo of ultrasound exposure, rapid bone growth with radiographic bridging of the bone defect was observed, and the external fixator was removed. The fracture was completely consolidated 3 mo after the initiation of the ultrasound treatment.

BIOPHYSICAL EFFECTS OF ULTRASOUND AND BONE OSTEOGENESIS

Experimental and clinical data prove that bone tissue metabolism is sensitive to the micromechanical strains induced by the acoustic pressure waves of LIPUS. Different hypotheses have been made to explain the exact mechanisms through which LIPUS acts on osteogenesis.

Histologic studies show that LIPUS influences all major cell types involved in bone healing, including osteoblasts, osteoclasts, chondrocytes and mesenchymal stem cells. The effect of LIPUS seems to be limited to cells in soft tissue, whereas cells in calcified bone seem not to be affected.

Even though the energy used by LIPUS treatment is low, the effects are evident. Cell cultures and research on experimental fractures in animal models have demonstrated changes in cytokine release (Li et al. 2003), in aggrecan gene expression (a proteoglycan involved in enchondral osteogenesis) (Wu et al. 1996) and in calcium cellular uptake (Rubin et al. 2001). In addition to modulating gene expression, ultrasound may enhance angiogenesis and increase blood flow around the fracture (Rawool et al. 1998). The biophysical mechanisms that may explain the above mentioned biochemical phenomena are not completely elucidated and may include the following: Minimal temperature increase (<1°C) (Chang et al. 2002), associated with energy absorption, may affect some enzymes such as matrix metalloproteinase 1 (collagenase 1) (Welgus et al. 1981, 1985).

LIPUS may induce a micromechanical stimulation of the bone and induce osteogenesis, according to

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Fig. 1. (A) A 45-year-old man who was in a car accident. Gustilo I exposed diaphyseal fracture of the tibia and fibula, treated with endomedullary nailing. Septic complication (*Staphylococcus aureus*). X-ray 7 mo after trauma. No sign of callus progression. Starts low-intensity pulsed ultrasounds LIPUS (FAST, IGEA S.r.l.), 20 min/d. (B) X-ray 11 mo after trauma; 4 mo from starting LIPUS. Note callus progression. (C) X-ray 18 mo after trauma. After nail removal and complete bone healing.

Wolff's Law (Wolff 1892). In particular, the differential absorption of LIPUS may establish a gradient of mechanical strain in the healing callus that stimulates periosteal bone formation (Gross et al. 1997; Rubin et al. 2001).

Cavitation mechanisms induced by ultrasound (500 mW/cm^2) increase protein (Harvey et al. 1975; Webster et al.1978) and collagen synthesis (Webster et al. 1980) in human fibroblasts *in vitro* and affect diffusion rates and membrane permeability (Mortimer et al. 1988; Ryaby et al. 1991; Rawool et al. 2003). However, cavitation has never been adequately confirmed in tissues.

CONCLUSIONS

Ultrasound has a significant effect on biological tissues and cells involved in bone healing and in fracture repair and data from the literature support a positive effect on osteogenesis of LIPUS, applied percutaneously, in different experimental and clinical settings. LIPUS significantly stimulates and accelerates fresh fracture healing and is effective in promoting bone healing in aseptic and septic delayed- and nonunions. On the basis of the available studies, LIPUS was approved for the treatment of fresh fractures in 1994 and of established nonunions in February 2000, while reimbursement from different national or regional public or private payers is currently available in many European Countries.

Even though the energy used by the LIPUS treatment is low, effects on cells *in vitro* and *in vivo* have been described but the detailed biophysical process by which LIPUS stimulates bone healing still remains unknown.

Advantages and limits of LIPUS applied to nonunions may be summarized as follows:

Advantages

1. Efficacy. Reported union rate ranges from 70% to 93%. The earlier the treatment is started, the better the results. High risk patients and long-lasting nonunions have the worst results. Outcomes may differ in different bones and hosts (Jingushi et al. 2007; Rubin et al. 2001).
2. Safety. No side effects related to the low-intensity pulsed ultrasound LIPUS has been reported, even in the presence of metallic device, osteosynthesis and infection.
3. Conservative. LIPUS is a conservative treatment that may avoid the need for additional complex operation.
4. Compliance. LIPUS is a home, low time-consuming, treatment, easy to perform and self-administered by the instructed patient.
5. Cost/benefit. Delayed- and nonunions increase dramatically the total cost of a fracture. LIPUS, as a home therapy and a conservative treatment that may lead to healing 8 out of 10 patients, has been shown to be a potential source of significant healthcare costs saving and has a positive cost/benefit ratio. Considering the incidence of delayed unions and nonunions in tibia fractures, Heckman and Sarasohn-Kahn (1997) recommended the use of LIPUS as an adjunctive treatment, estimating an overall cost savings of approximately US$ 13,000 to 15,000 per case.

Limits

1. Long time to healing. The average time to healing (3 to more than 6 mo) remains long, even if most of possible alternative surgical procedures are not generally connected with significantly earlier results.
2. Lack of randomized, controlled studies. Case series studies regarding the efficacy of LIPUS for delayed- and nonunions do not have a parallel control group, nor are they blinded, thus, raising the potential for bias. This limit is shared with all the available treatments of nonunions, including surgery. The large variability of fracture site, initial fracture severity and treatment, number of previous surgical interventions and host's type make extremely difficult to design a randomized study and to compare homogeneous series of patients.
3. Indication to use. The results of LIPUS in the treatment of nonunions depend largely on correct indications. Unstable fractures or synthesis, bone loss larger that 15 mm, severe torsional or axial deformity, large soft tissue defects and low patient's compliance, are among the most common contraindications to the treatment.

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