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J Bone Joint Surg Am. 83:259-, 2001.

THE JOURNAL OF BONE & JOINT SURGERY · JBJS.ORG | VOLUME 83-A · NUMBER 2 · FEBRUARY 2001

CURRENT CONCEPTS REVIEW

THE USE OF LOW-INTENSITY ULTRASOUND TO ACCELERATE THE HEALING OF FRACTURES

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- Double-blind, prospective, placebo-controlled clinical trials demonstrate that healing times of fresh fractures of the radius and tibia are reduced by up to 40% with the use of low-intensity ultrasound.
- Animal studies indicate that low-intensity ultrasound exposure results in stronger and stiffer callus formation and in acceleration of the endochondral ossification process.
- Extensive clinical evidence demonstrates that ultrasound represents a safe, noninvasive method of accelerating the healing of fresh fractures of the tibia, the distal aspect of the radius, the scaphoid, and the metatarsals.
- Clinical studies indicate that ultrasound reduces the confounding effect of smoking and patient age on the fracture-healing process.
- Ultrasound requires a brief, twenty-minute, daily at-home treatment regimen and has no known contraindications.
- The effectiveness of low-intensity ultrasound has also been demonstrated in the clinical treatment of delayed unions and nonunions.

Fracture-healing is a complex biological process that involves the spatial and temporal orchestration of numerous cell types, hundreds if not thousands of genes, and the intricate organization of an extracellular matrix, all working toward restoring the bone's mechanical strength and rapid return to full function. It has often been argued that nature has optimized this process and thus it would be difficult to interventionally accelerate or augment fracture-healing. How can science conceivably improve upon 600 million years of vertebrate evolution? Nevertheless, it is just this goal that has inspired an intense effort among basic-science and clinical investigators from a vast array of biotechnology and bioengineering disciplines at academic as well as industrial laboratories, to seek a means of accelerating the healing of fractured bones. In this article, the basic-science and clinical evaluation of the use of low-intensity ultrasound is reviewed and the case is made that nature's process of fracture-healing, while elegant, can be accelerated with respect to achieving the ability to support clinically relevant loads.

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 first regulatory approval was based primarily upon two rigorous, double-blind, placebo-controlled clinical trials, which showed that the rate of healing of fresh fractures is accelerated by treatment with ultrasound[1,2]. In concert with these clinical studies, substantive basic-science data demonstrated that ultrasound has a strong positive influence on each of the three key stages of the healing process (inflammation, repair, and remodeling) because it enhances angiogenic, chondrogenic, and osteogenic activity. Complementing the basic-science and clinical data is accumulating evidence that ultrasound has a role in the treatment of delayed unions and nonunions as well as in the reduction of overall cost factors that ultimately must be considered in the clinical-outcome equation.

Biomedical Applications of Ultrasound

Ultrasound, a form of mechanical energy that is transmitted through and into biological tissues as an acoustic pressure wave at frequencies above the limit of human hearing, is used widely in medicine as a therapeutic, operative, and diagnostic tool[3,4]. Therapeutic ultrasound, and some operative ultrasound, uses intensities as high as 1 to 3 W/cm^2 and can cause considerable heating in living tissues. To take full advantage of this energy absorption, physical therapists often use such levels of ultrasound acutely to decrease joint stiffness, to reduce pain and muscle spasms, and to improve muscle mo-

bility[5]. The use of ultrasound as a surgical instrument involves even higher levels of intensity (5 to 300 W/cm^2), and sharp bursts of energy are used to fragment calculi, to initiate the healing of nonunions, to ablate diseased tissues such as cataracts, and even to remove methylmethacrylate cement during revision of prosthetic joints[6].

At the opposite end of the ultrasound-intensity spectrum, much lower magnitudes of 1 to 50 mW/cm^2 are used to drive diagnostic devices that noninvasively image vital organs, fetal development, peripheral blood flow, and metabolic bone diseases such as osteoporosis[7] and, coincidentally, to evaluate fracture callus during healing[8,9]. The intensity level used for imaging, which is five orders of magnitude below that used for surgery, is regarded as nonthermal and nondestructive[10]. Nevertheless, low-intensity ultrasound is still a mechanical force, and it therefore holds the potential to influence bone mass and morphology through bone tissue's strong sensitivity to physical stimuli.

Just before the turn of the twentieth century, Wolff[11] demonstrated a phenomenological relationship between the architecture of cancellous bone and the inferred locomotory forces acting upon the skeleton. Recent work supports Wolff's conclusion that the form and architecture of bone adapt to the mechanical environment by remodeling to accommodate the magnitude and direction of the applied stress[12]. This relationship is frequently referred to as Wolff's law. While beyond the scope of this review, it is important to relate the mechanical basis of ultrasound to the sensitivity of bone tissue to mechanical stimuli. Several authors have provided insight into the possible mechanisms involved in bone's response to physiological mechanical force-loading[13,14], including the stimulation of vascular activity[15]. Therefore, the acoustic pressure waves generated by the ultrasound signal, at least in theory, represent a noninvasive means of influencing the healing of fractures by providing a surrogate for the forces at work in Wolff's law without raising an element of structural risk to the wound-healing process[16].

At one level, the acoustic pressure wave induced by ultrasound is indicative of a mechanical signal that takes full advantage of bone tissue's sensitivity to low-level physical signals. However, this acoustically driven mechanical signal is several orders of magnitude lower than the peak strains generated by functional load-bearing[17], while the rates of loading induced by ultrasound are several orders of magnitude higher. Nevertheless, extremely low-level, high-frequency mechanical signals persist in functionally loaded bone[18] and represent strong regulatory signals to skeletal tissue[19], even during fracture-healing[20].

The difficulty in determining how low-level ultrasound interacts with bone and connective tissue lies in the complex response of living tissue to these high-frequency acoustic stimuli. On passing through the tissue, the ultrasonic energy is absorbed at a rate proportional to the density of the tissue. Thus, the radical changes in density inherent in a healing callus may well establish gradients of mechanical strain, recognized as strong determinants of bone-modeling[21]. Absorption of the ultrasound signal also results in energy conversion to heat[22]. While this heating effect is extremely small, well below 1°C, some enzymes, such as MMP-1, or collagenase, are exquisitely sensitive to small variations in temperature[23]. Therefore, ultrasound may serve to reestablish or normalize effective metabolic temperatures in areas such as the distal parts of the extremities or in regions where blood flow has been compromised; this effect, while subtle, may be biologically profound[24]. Furthermore, at interfaces of distinct densities, such as at bone-callus surfaces, much of the incident radiation energy will be reflected, resulting in complex gradients of acoustic pressure through the tissue[25].

The differential energy absorption of ultrasound also gives rise to the phenomenon of acoustic streaming, or the movement of fluid across surfaces, particularly in regions where major quantities of bulk fluid are found. This acoustic streaming and the resultant fluid flow[26] may mechanistically advance signal-transduction pathways, a process referred to as mechanotransduction[27]. Thus, the introduction of an ultrasound signal stimulates a dynamic physical environment at the healing site. At its most basic mechanical level, the enhanced movement of fluid increases nutrient delivery and waste removal. It is likely that the acoustic signal is recognized and is strongly influential in the biology of bone cells and their progenitors. Regardless of its form, ultrasound results in mechanical perturbation of the tissues within its path. This of course inextricably links ultrasound to Wolff's law, the "form follows function" foundation of orthopaedics. Whether such low-level signals are biologically relevant, however, must be determined in *in vitro* and *in vivo* systems as well as in the clinical setting.

First Evidence of Ultrasound's Influence on Fracture-Healing

In 1952, investigators in Italy demonstrated, in a controlled, paired study of radial fractures in rabbits, that continuous-wave ultrasound could stimulate the formation of bone callus[28]. These findings led to the first clinical use of ultrasound to stimulate fracture-healing, and, in 1953, the same investigators found, in a study of eight patients, that the treatment was safe and produced an increase in periosteal callus[29]. More than thirty years later, Dyson and Brookes[30], in a study of bilateral fibular fractures in rats, demonstrated accelerated fracture-healing when treatment with 500 mW/cm^2 of pulsed ultrasound was compared with no therapy. These investigators found that ultrasound treatment was most effective during the early stages of healing. Extrapolating these data to the clinical setting, Xavier and Duarte[31] reported, in a Brazilian orthopaedic journal, that 70% of twenty-six nonunions healed after brief exposure (20 min/day) to very low-intensity ultrasound (30 mW/cm^2). This intervention was pursued as a means of mechanically stimulating the fracture site without the need for actual weight-bearing; it was hoped that ultrasound would provide the biological benefit of weight-bearing without jeopardizing the skeletal structure. In an effort to determine the optimum signal parameters, Duarte[32], using histological studies and radiographs, demonstrated that ultrasound signals identical to those used to treat nonunions in humans successfully accelerated cortical bridging across the site of a fibular osteotomy in rabbits by 28% compared with that in controls. These data suggest that ultrasound accelerated heal-

ing by stimulating the production of more callus and that the process of mineralization occurred earlier when the osteotomy site was exposed to low-intensity ultrasound.

These original findings were soon supported by Reuter et al.[33,34], who found positive effects in bone in a series of animal studies that involved the use of a continuous ultrasound signal that was an order of magnitude higher than that used by Duarte[32]. Klug et al.[35,36] demonstrated that ultrasound treatment, delivered at an intensity of 200 mW/cm^2, accelerated the healing of closed lower-extremity fractures in rabbits by 18%. Pilla et al.[37], in a placebo-controlled study of mid-shaft tibial osteotomies in rabbits, found that brief periods (20 min/day) of pulsed ultrasound (a 200-μs burst of 1.5-MHz sine waves, repeated at 1 kHz), delivered at a low intensity of 30 mW/cm^2, accelerated the recovery of torsional strength and stiffness. By the seventeenth day, each fracture that had been treated with ultrasound was as strong as an intact fibula. In contrast, the contralateral (control) limbs did not attain full strength until twenty-eight days after the osteotomy. That study indicated that bones that were exposed to ultrasound achieved biomechanical integrity in essentially half the time as untreated bones. Whether this was achieved by accelerating the process of mineralization (resulting in stiffer material) or by augmenting the size of the callus (resulting in more material) was not clear. Because the influence of the signal on healing was shown in distinct models and the work was performed in different laboratories, these independent validations add credibility to the premise that ultrasound may enhance the biological repair process.

Several years later, Wang et al.[38], in an effort to define the most efficacious signal parameters, studied the healing of bilateral closed femoral shaft fractures in rats. Those authors found that pulsed ultrasound (a 200-μs burst of 1.5 or 0.5-MHz sine waves, repeated at 1 kHz), delivered at an intensity of 30 mW/cm^2 for 15 min/day, increased bone strength at the fracture site. Within three weeks, the maximum torque to failure of the femora that had been treated with either the 1.5 or the 0.5-MHz burst was an average of 22% greater than that of the contralateral, control femora. The selectivity of the response was also apparent; the 32% increase in stiffness in the group treated with the 0.5-MHz burst was not significantly different from the increase in the controls, whereas the 67% increase in stiffness in the group treated with the 1.5-MHz burst was significantly greater than the increase in the controls ($p < 0.02$).

The sensitivity of the biological response to specific characteristics of the ultrasound signal was further supported by the findings of Jingushi et al.[39]. Those investigators, using a femoral fracture model in rats, demonstrated that low-intensity pulsed ultrasound improved several aspects of the healing process; specifically, it led to increases in bone-mineral content, bone-mineral density, peak torque, and stiffness as well as to the more rapid appearance and maturation of the overall endochondral ossification process. Jingushi et al. also found that a pulse width of 200 μs was more effective in enhancing fracture-healing than a pulse width of either 100 or 400 μs and that a 1-kHz repetition rate was more osteoinductive than one of 2 kHz. These results support the earlier findings[32,37] that a 200-μs pulse and a 1-kHz repetition rate are reflective of optimal ultrasound parameters for the healing of fractures. Nolte et al.[40], using these optimal signal parameters, studied the influence of low-intensity ultrasound on the endochondral ossification process in seventeen-day mouse metatarsal rudiments *in vitro*. The ultrasound-treated rudiments demonstrated a significant increase in the length of the calcified diaphysis compared with untreated controls ($p < 0.006$).

In an attempt to determine if the influence of ultrasound is greatest at some specific stage of fracture-healing, Azuma et al.[41] investigated the effect of the timing of low-intensity ultrasound treatment in a bilateral closed femoral fracture model in rats. The fracture sites were stimulated at four different time-periods (days 1 through 8, days 9 through 16, days 17 through 24, and days 1 through 24), and all animals were killed on day 25. Interestingly, union was accelerated in each group regardless of the duration or timing of the treatment. These results were confirmed by radiographs, histological studies, and mechanical strength measurements. The maximum torque to failure on the treated side was greater than that on the control side at all time-periods. These data suggest that, although the biology of fracture-healing can be accelerated, no specific stage of healing is more sensitive than another.

Glazer et al.[42], in an effort to examine the potential of ultrasound to influence healing in the spine, recently reported the biomechanical and histological characteristics of posterolateral spinal fusion in a rabbit model. Their findings indicated that ultrasound increased the rates of fusion, stiffness, and load to failure, suggesting an influence on the healing of both trabecular and cortical bone. Histological assessment confirmed that there was increased bone formation in the fusion masses that had been exposed to ultrasound. While these results are preliminary, they suggest that the low-level mechanical signal may influence cellular processes in the axial as well as the appendicular skeleton.

In a study of the potential of ultrasound to accelerate the maturation of regenerate callus, Mayr et al.[43] used low-intensity ultrasound in a placebo-controlled, segmental-transport callus distraction model in the metatarsals of sheep. The ultrasound-treated limbs showed a significant increase in bone-mineral content on quantitative computed tomography ($p < 0.05$), increased stiffness on nondestructive axial tests ($p < 0.01$), and increased bone formation on both static and dynamic histomorphometric analyses ($p < 0.01$).

Shimazaki et al.[44] recently investigated the effects of low-intensity pulsed ultrasound on distraction osteogenesis in a bilateral rabbit-tibia model in which two different distraction rates were used. In the first group, the limbs were distracted at a rate of 1 mm/day for ten days (total distraction, 10 mm) and then were tested at seven, fourteen, and twenty-one days after the cessation of distraction. Compared with the untreated limbs, the limbs that had been treated with low-intensity ultrasound had significantly higher values for hard-callus area at day 10 ($p < 0.01$), day 14 ($p < 0.001$), and day 17 ($p < 0.01$); for bone-mineral density ($p < 0.05$); and for mechanical strength at day 7 ($p < 0.01$) and day 14 ($p < 0.05$). Histological analysis showed no tissue damage that was attributable to the ultra-

TABLE I The Effects of Ultrasound on *in Vitro* Cell Model Systems

Study	Cell Model	Signal Intensity	Observed Effects
Chapman et al., 1980[45]	Thymocytes	0.5-3 W/cm^2 2 W/cm^2	Decreased intracellular K^+ ions, decreased K^+ ion uptake, increased K^+ ion efflux
Ryaby et al., 1989[46]	Differentiating cartilage and bone-cell cultures	200 mW/cm^2	Increased Ca^+ incorporation
Ryaby et al., 1991[47], 1992[48]	MC3T3/TE85 osteoblastic cell-lines	20, 30, 45 mW/cm^2	Increased adenylate cyclase activity, increased expression of TGF-β
Wu et al., 1996[52]	Chondrocytes	50, 120 mW/cm^2	Increased aggrecan mRNA expression
Parvizi et al., 1997[49], 1999[53]	Chondrocytes	50-500 mW/cm^2	Increased release of intercellular Ca^+, increased aggrecan mRNA expression, increased proteoglycan synthesis
Kokubu et al., 1999[50]	MC3T3 osteblastic cell-line	30 mW/cm^2	Increased expression of PGE_2/COX-2
Ito et al., 2000[51]	SaOS-2 osteoblastic cell-line HUVEC endothelial cells	30 mW/cm^2	Increased PDGF-AB secretion

sound. In the second group, the distraction rate was increased threefold, to 3 mm/day, and the limbs were distracted for seven days (total distraction, 21 mm). Serial radiographs, made for forty-two days after the cessation of distraction, showed immature regenerate bone in the untreated limbs and demonstrated that the treated limbs had significantly higher values for hard callus at day 21 ($p < 0.05$) and at days 24 through 42 ($p < 0.01$). While these data are only preliminary, they indicate that, even in difficult circumstances, ultrasound can still effectively influence the mineralization process.

This broad spectrum of work, which spans approximately fifty years, demonstrates, at a phenomenological level, that low-intensity ultrasound can influence the process of fracture-healing and mineralization in animal models and that healing itself is remarkably sensitive to specific characteristics of the ultrasound signal. These studies do not, however, lend much insight into the biological mechanisms that facilitate these complex processes.

Influences of Ultrasound on Biological Processes

Ultimately, the mechanical stimulation inherent to ultrasound translates into a biological response. Wide-ranging studies at both the *in vitro* and *in vivo* levels have been used to probe the biological mechanisms responsible for the observed influence of ultrasound on fracture-healing (Table I). In one of the first such studies, Chapman et al.[45] reported that ultrasound induced a change in the rates of influx and efflux of potassium ions in rat thymocytes. Ryaby et al.[46-48] later reported that low-intensity ultrasound increased calcium incorporation in both differentiating cartilage and bone-cell cultures, reflecting a change in cell metabolism. This increase in second messenger activity was paralleled by the modulation of adenylate cyclase activity and transforming growth factor-β synthesis in osteoblastic cells. The influence of ultrasound on second messenger activity in primary chondrocytes was also reported by Parvizi et al.[49], who found, using a real-time assay, that the application of ultrasound at 50 mW/cm^2 increased the release of cellular calcium (Fig. 1). Kokubu et al.[50] showed that low-intensity ultrasound (30 mW/cm^2) increased prostaglandin-E_2 production through the induction of cyclooxygenase-2 mRNA in mouse osteoblasts, and they concluded that ultrasound exerts its influence in a manner similar to that of fluid shear stress and tensile force stimuli. More recently, Ito et al.[51] studied the effect of low-intensity ultrasound on growth-factor secretion in a coculture of human osteoblastic and endothelial cells and found that ultrasound increased the release of platelet-derived growth factor in the conditioned media.

While these experiments demonstrate the ability of ultrasound to influence cell activity, if the signal is ultimately going to influence the rate of healing then ultrasound must be shown to effect the expression of genes involved in the inflammation and remodeling stages of fracture repair. In support of this critical point, Wu et al.[52] demonstrated that exposure of cultured chondrocytes to low-intensity ultrasound stimulates an upregulation of aggrecan gene expression, which occurs earlier in the fracture-healing process. During chondrogenesis, this large chondroitin-sulfate molecule aggregates with hyaluronan, decorin, and biglycan, creating key proteoglycan-scaffolding elements for type-II collagen. Thus, even when only this specific gene is considered, ultrasound accelerates and ultimately augments the processes of callus formation. In support of these findings, Parvizi et al.[53] demonstrated that low-intensity pulsed ultrasound stimulates proteoglycan synthesis in rat chondrocytes by increasing aggrecan gene expression, which might explain the role of ultrasound in augmenting endochondral ossification and thus increasing the mechanical strength and overall repair of the fractured bone.

Yang et al.[54] used an *in vivo* bilateral femoral fracture model in rats[55] to examine gene activity during healing and found that low-intensity ultrasound (50 or 100 mW/cm^2) increased aggrecan gene expression. Importantly, by using each animal as its own internal control, direct comparisons between treated and untreated fractures could be made independent of biological variations among animals. By examining both biological and biomechanical parameters within a single

experimental design, Yang et al. were able to demonstrate a direct correlation between increased aggrecan gene expression and enhanced structural strength. Ultimately, a study of transgenic or knockout mice (genetically engineered mice lacking one specific gene) may provide more specific, mechanistic insight into the role of aggrecan in the healing process. Until then, however, these experiments provide important data on the temporal parameters of healing and how ultrasound may modulate them.

Not all of the impact of ultrasound need be identified at the molecular mechanistic level in order to ultimately benefit healing. Rawool et al.[56] demonstrated that low-intensity ultrasound, delivered over a ten-day period, stimulated a greater degree of vascularity at the site of ulnar osteotomies in dogs. While these investigators originally hypothesized that ultrasound would increase blood flow during treatment, increased blood flow was evident at the fracture site for an extended period after removal of the stimulus. This increased blood flow, monitored by high-resolution diagnostic ultrasound, was paralleled by greater callus formation and markedly improved blood-flow distribution around the fracture.

These data suggest that, in addition to modulating gene expression (molecular interaction), ultrasound may increase blood flow through the dilation of capillaries (structural intervention) and the enhancement of angiogenesis (cellular interaction). It is generally believed that greater blood flow serves as a principal factor in the acceleration of fracture-healing. Indeed, one of the main biological goals of the inflammatory response is to reestablish the blood flow to the injured area. The corollary to this observation is that anything that diminishes blood flow or oxygenation of the fracture site, such as the severity of the injury, smoking, circulatory problems, or diabetes, will potentially suppress the healing response. Again, a major benefit of ultrasound may be that it biologically and biophysically optimizes healing processes and promotes an idealized environment that is conducive to repair.

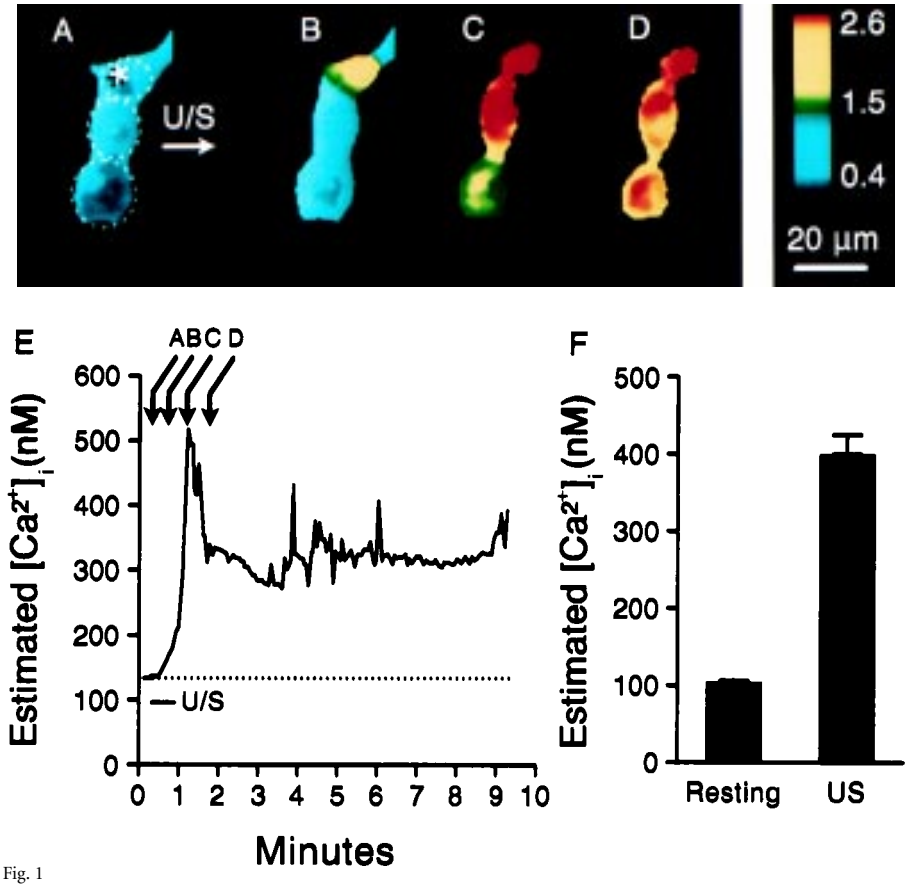

Fig. 1

A: Microscopic fluorescent images showing three chondrocyte cells (dotted circles), which have been cultured in a calcium medium and preloaded with fura-2/AM, a fluorescent marker that binds the calcium ion. *B, C,* and *D:* Images showing the increased release of intracellular calcium in response to the application of ultrasound at 50 mW/cm^2. *B* demonstrates the amount of released calcium (depicted as yellow in the topmost chondrocyte) in response to twenty seconds of applied ultrasound. *C* shows all three cells releasing calcium after approximately one minute of applied ultrasound. *D* shows increased amounts of calcium release in all three chondrocytes after two minutes of applied ultrasound. *E:* Graph showing the amount of calcium release from a single cell as a function of time, for a set level of ultrasound. *F:* Bar graph quantifying the amount of calcium released by the chondrocytes compared with the resting cells. (From: Parvizi J, Parpura J, Greenleaf JF, Bolander ME. Calcium signaling is required for ultrasound stimulated aggrecan synthesis by rat chondrocytes. Unpublished data.)

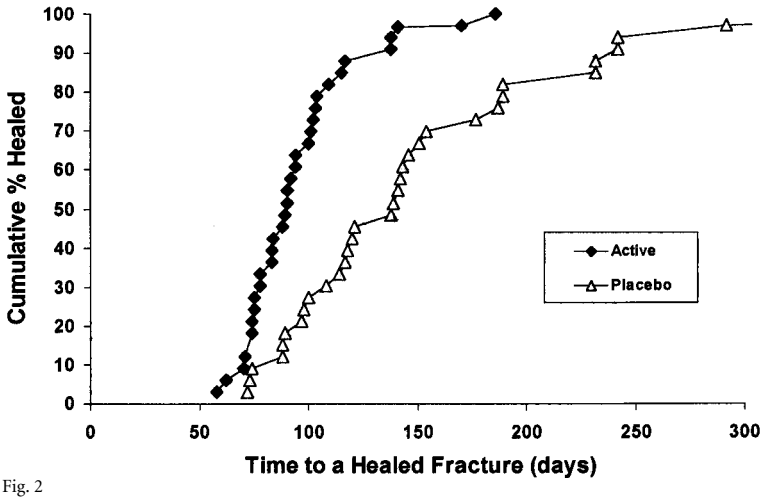

Fig. 2

Graph showing the cumulative percentages of clinically and radiographically healed tibial diaphyseal fractures in the core group as a function of time. The benefit in the group that received ultrasound is shown at ninety days after the fracture; 56% of the thirty-three fractures in that group healed compared with 18% of the thirty-three in the group treated with a placebo. One fracture in the group treated with a placebo healed at 465 days after the fracture, and no clinical data were available for one fracture in this group. The fractures in the ultrasound-treated group healed at a mean (and standard error) of 96 ± 4.9 days compared with 154 ± 13.7 days for the fractures in the placebo group ($p = 0.0001$; analysis of variance, rank analysis of variance, and log-rank life-table analysis). (From: Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF: Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. J Bone Joint Surg Am. 1994;76:26-34.)

The Ability of Ultrasound to Accelerate Fracture-Healing in the Clinical Setting

The broad spectrum of experiments performed at the basic-science level has provided substantial evidence that low-intensity ultrasound can accelerate and augment the fracture-healing process. However, the single most demanding evaluation of any proposed intervention must be performed at the clinical level. The use of ultrasound for the treatment of fractures has been evaluated in two multicenter, prospective, double-blind, placebo-controlled clinical trials.

In the first such study, Heckman et al.[1] performed a randomized, double-blind, placebo-controlled trial of sixty-seven closed or grade-I open tibial fractures to evaluate the effect of ultrasound on the healing of cortical fractures. Ultrasound treatment consisting of 30 mW/cm^2 for 20 min/day led to a significant (24%) reduction in the time to clinical healing (average, 86 ± 5.8 days in the treatment group compared with 114 ± 10.4 days in the control group; $p = 0.01$) as well as to a 38% decrease in the time to overall (clinical and radiographic) healing (average, 96 ± 4.9 days in the treatment group compared with 154 ± 13.7 days in the control group; $p = 0.0001$). The patients' compliance with daily use of the ultrasound device was high, and there were no complications related to its use. Cook et al.[57], in analyzing the data from fractures that were both clinically and radiographically healed in Figure 2 in the study by Heckman et al.[1], found that 36% (twelve) of the thirty-three fractures in the control group went on to delayed union compared with only 6% (two) of the thirty-three fractures in the treatment group ($p < 0.003$), suggesting that ultrasound exposure not only accelerates healing but may help to ensure healing. Perhaps it can be argued that an intervention that establishes a more rapid path to healing is welcome but not essential. It should also be argued, however, that an intervention that enhances the likelihood of healing makes an important contribution clinically.

In the second such study, Kristiansen et al.[2] performed a multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial of sixty-one dorsally angulated fractures of the distal aspect of the radius to determine the effect of ultrasound on the healing of fractures in areas consisting primarily of trabecular bone. The time to union was 38% shorter for the fractures that were treated with ultrasound for 20 min/day than it was for the fractures that were treated with a placebo (average, 61 ± 3 days compared with 98 ± 5 days; $p < 0.0001$) (Fig. 3). In addition, ultrasound treatment was associated with a significantly smaller loss of reduction (average, 20% ± 6% for the treatment group compared with 43% ± 8% for the control group; $p < 0.01$), an important morphological criterion for return to function following a fracture.

The influence of ultrasound on fracture-healing was supported by the findings of Mayr et al.[58], who performed a prospective, randomized, controlled, clinical trial of patients with fresh scaphoid fractures. The study group consisted of fifteen fractures that received standard treatment combined with low-intensity ultrasound for 20 min/day, and the control group consisted of fifteen fractures that received standard treatment only. Computerized tomography showed that the fractures in the study group healed 30% faster than those in the control group (average, 43.2 ± 10.9 days compared with 62 ± 19.2 days; $p < 0.01$). At six weeks, the trabecular bridging ratio was almost 50% higher in the study group than it was in the control group (average, 81% ± 10.4% compared with 55% ± 2.9%; $p < 0.05$).

Strauss et al.[59] performed a prospective, randomized study of twenty patients who had a fresh Jones fracture (a frac-

ture at the base of the fifth metatarsal) that was treated with standard orthopaedic technique with or without the addition of low-intensity ultrasound. All ten fractures that were treated with ultrasound healed both clinically and radiographically by fifty-six days after the injury. Of the ten fractures that were not treated with ultrasound, six healed by eighty-seven days, two healed by 112 days, and two still had not healed by twenty weeks after the injury.

The clinical use of ultrasound during limb-lengthening was first described, to our knowledge, by Sato et al.[60], who reported on a twenty-two-year old woman with short stature. A callotasis procedure and subsequent distraction at a rate of 1 mm/day increased the length of each tibia by 9 cm. Low-intensity ultrasound was then used on one limb, which accelerated the rate of callus formation. These results demonstrate that low-intensity ultrasound can have an accelerating effect on callus formation and maturation and may shorten the overall time to fixation removal in patients managed with limb-lengthening, who require a long period of treatment.

Importantly, not all studies have shown that ultrasound has a beneficial influence on fracture-healing. Emami et al.[61,62] recently reported the results of a prospective, randomized study in which reamed, internally fixed tibial fractures received active ultrasound (fifteen patients) or placebo treatment (seventeen patients). Those investigators found that low-intensity ultrasound had essentially no effect on healing. However, it is also important to note that there were several differences between this study and previous studies of tibial fractures. In the study by Heckman et al.[1], the fractures were treated with closed reduction and were immobilized in a cast until the physician thought that they were sufficiently stable that the cast could be removed, and the placebo or active treatment was continued for 140 days or until the fracture had healed. In contrast, all of the fractures in the studies by Emami et al.[61,62] were reamed and fixed with a tight-fitting locked rod, and the placebo or active treatment was continued for only seventy-five days. These data emphasize a very important point—namely, that ultrasound does not necessarily work in all orthopaedic conditions and does not necessarily benefit all healing processes.

Frankel[63] and Lane et al.[64] analyzed the patient registry of Exogen (Piscataway, New Jersey) as of July 1997 and January 1998, respectively, and found that ultrasound had been prescribed for many skeletal sites other than the radius or tibia and for patients with longer fracture ages (the time from the initial fracture to the start of low-intensity ultrasound treatment) than were reported in the previously mentioned clinical trials. Although the ultrasound device is indicated for fresh fractures of the tibia and the distal aspect of the radius, physicians have prescribed it for fractures of all ages and, in particular, for patients with comorbidities such as older age, diabetes, active smoking status, vascular insufficiency, and obesity[63-65]. Fracture-related comorbidities include the severity and grade of the fracture, the failure of previous procedures, and extensive soft-tissue damage due to displacement. The Exogen registry is maintained with physician input regarding the initial fracture and patient characteristics as well as the final outcome. An update of the registry by the authors, using the data-reporting format of Frankel[63], showed that, as of June 2000, low-intensity ultrasound treatment, applied at home for 20 min/day, had been prescribed for more than 22,300 patients. More than 1470 patients were lost to follow-up, an additional 1640 withdrew from treatment or were noncompliant with use of the ultrasound device, and more than 9100 patients were receiving active treatment. The remainder of more than 10,050 patients had a 91% rate of healing, an average healing time of 144 days (median, 120 days), and an average fracture

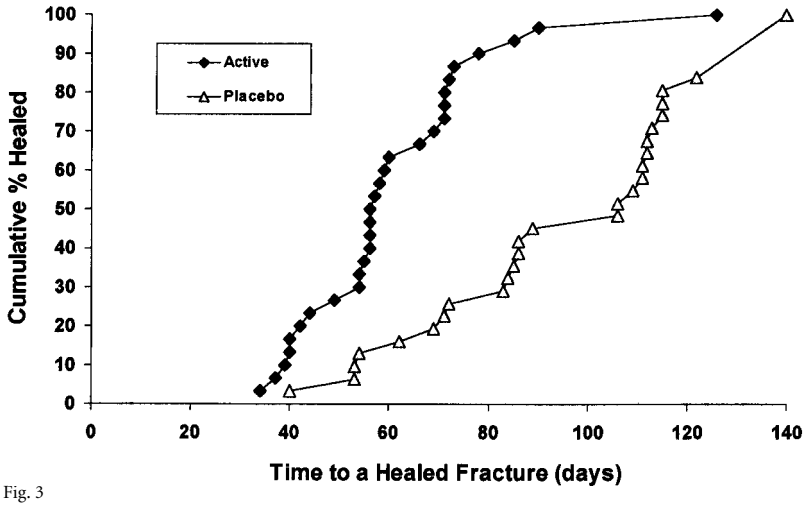

Fig. 3

Graph showing the cumulative percentages of healed distal radial fractures in the group treated with ultrasound compared with the group treated with a placebo. The benefit of treatment is seen well at seventy days after the fracture; approximately 70% of the thirty fractures in the ultrasound-treated group healed compared with 19% of the thirty-one in the group treated with a placebo. The fractures in the ultrasound-treated group healed at a mean (and standard error) of 61 ± 3.0 days compared with 98 ± 5.0 days for the fractures in the placebo group ($p < 0.0001$). (From: Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR: Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am. 1997;79:961-73.)

age of 168 days (more than five months) from the date of the initial injury. According to the clinical records and depending on the fracture-age group, between 80% and 90% of the patients had only ultrasound as the new treatment.

In the idealized situation, where the process of wound repair is already progressing as quickly as can be biologically sustained, subtle enhancement of blood flow may produce subtle shifts in the temporal expression of genes, and this may not be sufficient to influence the time to healing. However, an intervention that is able to normalize the process of healing may be of benefit in cases of severe injury and may help to enhance healing in patients in whom this process is normally suppressed, such as those who are elderly, those who have diabetes, and those who smoke. To identify risk factors that adversely affected fracture union, Lane et al.[64] analyzed the 2126 cases in the registry database that, as of January 1998, had a fracture age of less than 181 days. The overall rate of healing was 93.7%, and the average time to healing was 107 days. The rate of healing of fractures of the humerus was only 83%; this rate was significantly lower than the overall rate of 93.7% ($p < 0.001$). Univariate and multivariate analysis revealed that the rate of healing was reduced by a number of variables, including older patient age, older fracture age, smoking, obesity, steroid use, renal disease, and fracture of the humerus. Additional evidence of how the systemic status of the patient confounds healing was provided by Mayr et al.[65], who reviewed the registry database to assess the effect of comorbidities on fracture-healing in patients who had had low-intensity ultrasound for the treatment of delayed unions and nonunions. They found that the healing rate was decreased by 5% to 10% in patients taking calcium-channel blockers, nonsteroidal anti-inflammatory drugs, and steroids; in those being treated for renal disease; and in those with vascular insufficiency at the site of the nonunion[65]. With these compromised healing conditions, it becomes important to determine if ultrasound can somehow benefit patient outcomes.

Cook et al.[57] reported, in a further analysis of the data of Heckman et al.[1] and Kristiansen et al.[2], that the use of low-intensity ultrasound was associated with a significant reduction in the healing time of fractures of the tibia and the distal aspect of the radius in smokers. The average healing time for tibial fractures in smokers was reduced by 41%, from 175 ± 27 days to 103 ± 8.3 days ($p < 0.006$, analysis of variance). The average healing time for fractures of the distal aspect of the radius in smokers was reduced by 51%, from 98 ± 30.0 days to 48 ± 5.1 days ($p < 0.003$, analysis of variance).

Strauss and Gonya[66] described the effect of low-intensity ultrasound following ankle arthrodesis in two patients with Charcot arthropathy. One patient had a long history of diabetes and alcoholism and had had five prior failed operative procedures; the nonunion healed after 5.5 months of low-intensity ultrasound treatment. The other patient had a history of pancreatic disease and renal transplantation, two failed operative procedures, and failure of treatment with adjunct electrical stimulation; the nonunion healed after four months of ultrasound therapy.

These findings are important from two distinct viewpoints. First, they suggest that low-level biophysical stimuli can reestablish the normal rate and stages of healing that habits such as smoking typically disrupt. This is encouraging, as delays in these healing processes often result in nonunions. Second, they suggest that ultrasound can normalize healing in patients in whom the metabolic status is not ideal, and they may provide insight into the mechanisms by which this biophysical stimulus interacts with the biological system—that is, by counteracting the diminished efficiency of oxygen transport in smokers or that of angiogenesis in diabetic patients.

Evidence of the Influence of Ultrasound on Nonunions

The great majority of the basic-science and clinical data that have been reported thus far are related to the effect of ultrasound on the healing of fresh fractures. At the clinical level, these data include information from prospective, double-blind, placebo-controlled trials that have been performed to evaluate the efficacy of ultrasound in accelerating the healing of fractures of the tibia or radius as well as those at other sites, such as the femur, and those in patients with comorbidities, such as smoking. Nevertheless, a major clinical problem is the fracture that shows little healing after several months; indeed, between 5% and 10% of all fractures will eventually be classified as delayed unions or nonunions. Darder and Gomar[67] reviewed a series of 202 tibial fractures that had been treated conservatively and classified the fractures into eight types according to the initial displacement, the amount of comminution, and the severity of the wound. A total of 44% (eighty-eight) of the fractures were classified as delayed unions. Dickson et al.[68] retrospectively studied 114 open tibial fractures and found that 30% (thirty-four) were classified as delayed unions or nonunions.

Unfortunately, while adjunctive therapies such as electromagnetic stimulation or injection of growth factors have had some acceptance, they are not universally considered to be successful alternatives to surgery. Recent evidence demonstrates that the benefit of low-intensity ultrasound extends beyond its influence on fresh fractures. For example, building on the early application of low-intensity ultrasound therapy[31], Duarte et al.[69] reported an 85% healing rate and an average healing time of fourteen months in a study of 385 nonunions.

A number of independent studies[65,70-73] have recently examined the influence of ultrasound treatment on delayed unions and nonunions at a wide array of sites, such as the scaphoid, clavicle, ulna, femur, and metatarsals. While it is difficult to compare studies because of differences in the ways that the results might be analyzed, an overview of the data is valuable. For example, Mayr et al.[74] examined a group of twenty-nine patients with delayed union (average fracture age, 4.5 months) or nonunion (average fracture age, 2.9 years) and reported a healing rate of 88% and 93%, respectively, after approximately 100 days of ultrasound treatment. In another study, Mayr et al.[72] examined seventy-six nonunions (average fracture age, 10.5 months) and reported a healing rate of 86% after an average of five months of ultrasound treatment. That

TABLE II Registry Data on Nonunions (Completed Cases as of June 15, 2000)

Site of Nonunion*	No. That Healed	Average Time to Healing *(days)*	Average Fracture Age *(days)*
Femur	213 (82%) of 259	209	796
Humerus	102 (69%) of 148	176	660
Metatarsal	81 (89%) of 91	133	604
Radius or ulna	60 (87%) of 69	126	538
Scaphoid	101 (86%) of 118	139	613
Tibia or tibia and fibula	404 (84%) of 483	180	722

*Nonunion was defined as a lack of healing at more than 255 days.

article[72] included the case reports of three patients in whom the successful treatment of the nonunion could be attributed only to the ultrasound therapy.

Romano et al.[75] reported on fifteen patients with challenging cases of infected nonunions; there were ten nonunions of the tibia, two of the femur, and one each of the humerus, ankle, and ulna. The rate of healing was nine of ten among the completed cases, with the remaining five nonunions showing signs of progressive healing. In July 1997, Frankel[63] studied the registry database and assessed the overall healing rate among 404 nonunions at different bone sites. He reported a healing rate of 70% (forty of fifty-seven) for the humerus, 86% (seventy-three of eighty-five) for the femur, 81% (seventeen of twenty-one) for the metatarsals, 96% (twenty-three of twenty-four) for the radius, 86% (thirty-one of thirty-six) for the scaphoid, and 83% (151 of 181) for the tibia. The average time to healing ranged from 118 days for nonunions of the radius to 173 days for nonunions of the humerus, and the average fracture age was 1.8 and 1.6 years for the radial and humeral nonunions, respectively.

Investigators in the Netherlands evaluated the efficacy of ultrasound treatment, applied at home for 20 min/day, in a study of forty-one nonunions at multiple sites, including the tibia, femur, scaphoid, humerus, clavicle, and metatarsals[76]. Four cases withdrew early in treatment, leaving thirty-seven documented nonunion cases with a minimum fracture age of six months. The mean fracture age was 13.9 months, and the mean time from the start of ultrasound treatment to the last prior orthopaedic procedure was 9.1 months. The healing rate due to ultrasound treatment was 95% (thirty-five of thirty-seven), with a mean healing time of 130 days. Those cases with no surgery within the three months prior to the start of ultrasound treatment had a healing rate of 93% (twenty-six of twenty-eight), while those with surgery within the prior three months had a healing rate of 100% (nine of nine). Similar results were obtained in a French study of forty-four nonunions that were treated with low-intensity ultrasound[77]. The patients' history of failed operative treatments served as the control. The average number of failed operative procedures was 2.2, the average fracture age was 25.3 months, and the average time since the last operation was 6.3 months. Those investigators reported a rate of healing of 89% (thirty-nine of forty-four), with an average time to healing of six months. Specifically, there were twenty-five nonunions of the tibia (twenty-one of which healed), five of the femur (all of which healed), three of the knee (two of which healed), six of the radius/ulna (all of which healed), and one each of the ankle, clavicle, humerus, metacarpal, and shoulder (all of which healed).

Gebauer et al.[78], in a self-paired control study (that is, a study in which each nonunion served as its own control), assessed the efficacy of low-intensity ultrasound for the treatment of long-term nonunions. Sixty-seven established nonunions, with a minimum fracture age of eight months and a minimum of four months since the last operation, constituted the study group. All nonunions met stringent criteria for inclusion. The average fracture age was thirty-nine months, and the maximum fracture age was sixteen years. The study group had had an average of 2.0 prior failed procedures, and the average time from the last operation was 24.2 months. The only new treatment was the addition of low-intensity ultrasound. Following daily ultrasound treatment for an average of six months, 85% (fifty-seven) of the sixty-seven nonunions healed; this rate was significantly higher than the 0% rate of the prior failed treatment ($p < 0.00001$). These authors compared their results with those reported in a compilation of studies of nonunions in which operative intervention was used and concluded that low-intensity ultrasound provided outcomes similar to those of operative intervention but without the associated risks and complications.

Our review of the prescription-use registry as of June 2000 showed that the more than 5050 fresh fractures (zero to ninety days after injury) had a healing rate of 94%, the more than 1790 early delayed unions (ninety-one to 150 days after injury) had a healing rate of 91%, and the more than 1370 late delayed unions (151 to 255 days after injury) had a healing rate of 89%. The 1546 nonunions (more than 255 days after injury) had a healing rate of 83%, with an average time to healing of 172 days. When the nonunions (average fracture age, more than 1.9 years) were stratified by the major fracture location, the healing rate ranged from 69% for the humeral nonunions to 89% for the metatarsal nonunions (Table II).

These data suggest that ultrasound is a reasonable, noninvasive treatment for fractures that are likely to have delayed healing, for those not yet on a normal course of healing, or for those in patients whose metabolic status may be compromised by disease or medication.

Overview

On the basis of a broad spectrum of laboratory and clinical studies, several biological mechanisms (direct and indirect) have been proposed to explain the influence of ultrasound on the acceleration of the fracture-repair process. Data from various *in vitro* studies suggest that ultrasound may induce conformational changes in the cell membrane and thus alter ionic permeability[45,46] and second messenger activity[47,48]. Changes in second messenger activity could then conceivably lead to downstream alterations in gene expression, resulting in an acceleration of the fracture-repair process by upregulating cartilage and bone-specific genes as well as others. Rawool et al.[56] reported that ultrasound also stimulates angiogenesis, thus increasing blood flow to the fracture site and inherently delivering the key components, such as growth factors and cytokines, that are necessary for the normal healing process. Yang et al.[54] and Nolte et al.[40] suggested that ultrasound stimulates chondrogenesis and cartilage hypertrophy, resulting in an earlier onset of endochondral formation and thus leading to an increase in stiffness and strength of the fracture site, as noted by Wang et al.[38]. While the mechanism of ultrasound interaction with the wound response may not be defined, it is clear that the fracture-repair process is extremely complex and that a host of cells, genes, and other regulatory factors (for example, cytokines and functional load-bearing), many of which may be influenced by the ultrasound signal, work together during the healing process.

A large repository of basic-science and clinical work suggests a means by which fracture-healing can be augmented by low-intensity ultrasound. Considering the number of ways in which the healing process can be disrupted, a potential advantage of ultrasound treatment is that it does not overtly depend on a singular mechanism or on a single phase of the healing process. Instead, it appears to influence several aspects of the healing process in the inflammatory, reparative, and remodeling phases. Since the intervention is noninvasive, it could be argued that ultrasound represents a combination of conservative and aggressive treatment that encourages the normal process of healing.

That conclusion is supported by a recent study, by Heckman and Sarasohn-Kahn[79], on the economic benefits of treating tibial fractures with low-intensity ultrasound. Considering the number of these fractures that advance to nonunion, there could be an estimated overall cost-savings of between $13,000 and $15,000 per case (including the cost of the ultrasound therapy) associated with the use of low-intensity ultrasound.

The fracture-repair process is sophisticated yet primal, delicate yet robust. It involves many interdependent stages, and it relies on temporal and spatial orchestration of a wide array of genes and cell types. A complex injury, or a systemic state that compromises the healing process, is associated with a higher risk of delayed union and nonunion as well as with the potential for diminished function, and this accentuates the need to consider proven interventions. The use of ultrasound, through a variety of mechanisms, some biological and some physical, can culminate in a fracture-healing process that is both accelerated and augmented. Ultimately, however, ensuring that the process is completed is the most critical goal. ■

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One or more of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article. No funds were received in support of this study.

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