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INTRODUCTION: There are no previous reports of low intensity pulsed ultrasound therapy in connection with bioabsorbable fracture fixation. In this randomised, prospective, double-blind and placebo-controlled study, the effects of ultrasound on bone mineral density and bone healing were examined in lateral malleolar fractures fixed with a bioabsorbable self-reinforced poly-L-lactide screw (SR-PLLA).

MATERIALS AND METHODS: Thirty adult patients with SR-PLLA screw-fixed lateral malleolar fractures underwent ultrasound therapy 20 min daily for 6 weeks. Half of the patients were provided randomly with a sham ultrasound device. Bone mineral density and bone healing were assessed by dual-energy X-ray absorptiometry (DXA) and by radiographs.

RESULTS: Bone mineral density of the fractured lateral malleolus tended to increase slightly during 12 weeks of follow-up. The increase was symmetrical and statistically non-significant between the ultrasound and non-ultrasound group. All the fractures healed uneventfully. The biocompatibility of the bioabsorbable SR-PLLA fixation device and low intensity pulsed ultrasound was good. Despite the slight tendency for more frequent callus formation in the ultrasound group, no statistically significant effect of low intensity pulsed ultrasound on lateral malleolar fracture healing could be observed.

CONCLUSION: It was not possible to observe any statistically significant effect of low intensity pulsed ultrasound on lateral malleolar fracture healing in this study. Further studies are needed to examine the role of ultrasound therapy in the healing of fractures treated with bioabsorbable fixation devices.

Ultrasound therapy for the prevention and correction of contractures and bone mineral loss associated with wing bandaging in the domestic pigeon (Columba livia).

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Figure-of-eight wing bandaging is widely used to treat wing injuries, to immobilize wings before and after fracture repair, and during transient wing paralysis. However, prolonged bandaging can lead to bone loss and to contractures and reduced range of joint motion. Studies evaluating the efficacy of therapeutic ultrasound to reverse and prevent bandaging-associated contractures in pigeons (Columba livia) showed a significant increase in elbow and carpal extension after 10 twice weekly ultrasound treatments when started either 4 or 11 days after bandage placement. In addition, after 42 days of wing bandaging, three ultrasound treatments stimulated a faster reversal of carpal wing rotation loss than removal of the bandage over the 10-day treatment period. Finally, bone loss in response to 28 days of bandaging was significant, progressed at 2.8% per week, and was not affected by ultrasound treatment twice weekly during this period. Therefore, therapeutic ultrasound prevented and reversed loss of wing extension associated with figure-of-eight bandaging but did not lessen the disuse osteoporosis created by bandaging in these birds.
The effect of low-intensity pulsed ultrasound on bone healing in SR-PLLA rod fixed experimental distal femur osteotomy in rat.

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The effects of low-intensity pulsed ultrasound (30 mW/cm²) were investigated in experimental cancellous bone fracture healing in bioabsorbable self-reinforced poly-L-lactide (SR-PLLA) rod fixed distal femur osteotomy in rats. A transverse transcondylar osteotomy was fixed with one SR-PLLA rod in 32 male Wistar rats of the age of 20 weeks. Half of the rats had a daily 20-min ultrasound exposure for three weeks. The follow-up times were three, six, and 12 weeks. Radiographical, histological, microradiographical, oxytetracycline labeling, and histomorphometrical analyses were performed. No foreign-body reactions were noted. The biocompatibility of SR-PLLA and ultrasound was found to be good. In the radiological and histological assessments there was a slight tendency for enhanced healing in the ultrasound group at three weeks, but at six and 12 weeks no differences were observed. The histomorphometrical and oxytetracycline labeling analyses showed that ultrasound exposure had no significant effects on bone healing. The present study shows that there were no obvious findings to support the hypothesis that low-intensity pulsed ultrasound enhances bone healing in self-reinforced poly-L-lactide (SR-PLLA) rod fixed experimental metaphyseal distal femur osteotomy in rats. The observed good biocompatibility provides a safe starting-point for clinical trials on bioabsorbable fixation combined with low-intensity ultrasound.

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The effects of low-intensity pulsed ultrasound on bioabsorbable self-reinforced poly L-lactide screws.

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The effects of low-intensity pulsed ultrasound on the mechanical and molecular properties of self-reinforced poly L-lactide (SR-PLLA) screws were studied in vitro. SR-PLLA screws of 4.5 mm diameter were exposed on low-intensity ultrasound for 1, 3, 6, 9, and 12 weeks. After exposure, the bending strength, shear strength, and molecular weight were investigated. There were no differences in the investigated properties between the ultrasound exposure and control groups. We found no evidence that low-intensity ultrasound has any effect on the mechanical or molecular properties of SR-PLLA screws in vitro. The present results suggest that biodegradable SR-PLLA fixation devices are compatible with low-intensity ultrasound in vitro.

Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study.

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A multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial was conducted to test the efficacy of a specifically programmed, low-intensity, non-thermal, pulsed ultrasound medical device for shortening the time to radiographic healing of dorsally angulated fractures (negative volar angulation) of the distal aspect of the radius that had been treated with manipulation and a cast. Sixty patients (sixty-one fractures) were enrolled in the study within seven days after the fracture. The patients used either an active ultrasound device (thirty fractures) or a placebo device (thirty-one fractures) daily for twenty minutes at home for ten weeks. The two types of devices were identical except that the placebo devices emitted no ultrasound energy. Clinical examination was performed and radiographs were made at one, two, three, four, five, six, eight, ten, twelve, and sixteen weeks after the fracture by each site investigator. The time to union was significantly shorter for the fractures that were treated with ultrasound than it was for those that were treated with the placebo (mean [and standard error], 61 +/- 3 days compared with 98 +/- 5 days; p < 0.0001). Each radiographic stage of healing also was significantly accelerated in the group that was treated with ultrasound as compared with that treated with the placebo. Compared with treatment with the placebo, treatment with ultrasound was associated with a significantly smaller loss of reduction (20 +/- 6 per cent compared with 43 +/- 8 per cent; p < 0.01), as determined by the degree of volar angulation, as well as with a significant decrease in the mean time until the loss of reduction ceased (12 +/- 4 days compared with 25 +/- 4 days; p < 0.04). We concluded that this specific ultrasound signal accelerates the healing of fractures of the distal radial metaphysis and decreases the loss of reduction during fracture-healing.

Low-intensity pulsed ultrasound in the treatment of nonunions

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BACKGROUND: Low-intensity ultrasound has demonstrated an acceleration of bone healing and more profound callus formation in animal and human clinical experiments. In this study, the effect of pulsed, low-intensity ultrasound was determined in established nonunion cases. METHODS: The enrolled cases were reviewed for the time from their last surgical procedure and evidence of no healing or progression of healing during the 3 or more months before the start of low-intensity ultrasound therapy to determine whether the cases were established nonunions. Twenty-nine cases, located in the tibia, femur, radius/ulna, scaphoid, humerus, metatarsal, and clavicle, met the criteria for established nonunions. On average, the postfracture period before the start of ultrasound treatment was 61 weeks. Initial fracture treatment was conservative in 8 cases and operative in 21 cases. Additional treatments including bone grafting, reosteosynthesis, and other surgical procedures were performed an average of 52 weeks before the start of ultrasound treatment. Daily, 20-minute applications of low-intensity ultrasound at the site of the nonunion were performed by the patients at home. RESULTS: Twenty-five of the 29 nonunion cases (86%) healed in an average treatment time of 22 weeks (median, 17 weeks). Stratification of the healed and failed outcome for age, gender, concomitant disease, bone location, fracture age, prior last surgery interval, nonunion type, smoking habits, and fixation before and during treatment showed a significant difference only in the smoking habit strata. CONCLUSION: Noninvasive ultrasound therapy can be useful in the treatment of challenging, established nonunions.

Low intensity ultrasound effects over osteopenic female rats bones

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Several studies have already shown the beneficial effects of low intensity pulsed ultrasound on osteogenesis in fracture cases. However, few reports have related the ultrasound action in bone with some injury but without fracture. Thus, we induced a rat osteopenia model by ovariectomy and the proximal third of rat femur was stimulated by ultrasound (200ms burst of 1.5 MHz sine waves repeated at 1.0 kHz, 30mW/cm², SATA) for 20 min/day, during 20 days.

After the treatment period, the body weight was significantly higher in the non-treated group than the treated one. No significant difference in bone mineral content was detected among the groups (p > 0.05). Also, no significant difference was noted in the mechanical properties of the femoral diaphysis. However, histologic investigations showed that the treated femur presented less microarchitectural deterioration than the non-treated group. Moreover, it was demonstrated that the treated group did show recent bone formation which was not there in the non-treated group. These results suggest that the low intensity ultrasound can interfere in a positive way on osteoporosis.


**Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula.**

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INTRODUCTION: Low-intensity pulsed ultrasound (LIPUS) accelerates impaired fracture healing, but the exact mechanism is unknown. The aim of this study was to investigate how LIPUS affects bone healing at the tissue level in patients with a delayed union of the osteotomized fibula, by using histology and histomorphometric analysis to determine bone formation and bone resorption parameters. MATERIALS AND METHODS: Biopsies were obtained from 13 patients (9 female, 4 male; age 42-63) with a delayed union of the osteotomized fibula after a high tibial osteotomy, treated for 2-4 months with or without LIPUS in a randomized prospective double-blind placebo-controlled trial. In the histological sections of the delayed union biopsies, 3 areas of interest were distinguished, i.e. 1) area of new bone formation at the fracture ends, 2) area of cancellous bone, and 3) area of cortical bone. Histomorphometrical analysis was performed to determine bone formation and bone resorption parameters (as well as angiogenesis). RESULTS: In LIPUS-treated delayed unions, endosteal callus formation by direct bone formation without a cartilage intermediate as well as indirect bone formation was observed, while in untreated controls only indirect bone formation was observed. In the area of new bone formation, LIPUS significantly increased osteoid thickness by 47%, mineral apposition rate by 27%, and bone volume by 33%. No increase in the number of blood vessels was seen in the newly formed bony callus. In the area of cancellous bone, bone volume was significantly increased by 17% whereas no effect on osteoid thickness and mineral apposition rate was seen. LIPUS did not affect osteoid volume, osteoid maturation time, number of osteocytes, osteocyte lacunae, or osteoclast-like cells in any of the areas of interest. CONCLUSIONS: Our results suggest that LIPUS accelerates clinical fracture healing of delayed unions of the fibula by increasing osteoid thickness, mineral apposition rate, and bone volume, indicating increased osteoblast activity, at the front of new bony callus formation. Improved stability and/or increased blood flow, but probably not increased angiogenesis, might explain the differences in ossification modes between LIPUS-treated delayed unions and untreated controls.

Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound.

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Sixty-seven closed or grade-I open fractures of the tibial shaft were examined in a prospective, randomized, double-blind evaluation of use of a new ultrasound stimulating device as an adjunct to conventional treatment with a cast. Thirty-three fractures were treated with the active device and thirty-four, with a placebo control device. At the end of the treatment, there was a statistically significant decrease in the time to clinical healing (86 +/- 5.8 days in the active-treatment group compared with 114 +/- 10.4 days in the control group) (p = 0.01) and also a significant decrease in the time to over-all (clinical and radiographic) healing (96 +/- 4.9 days in the active-treatment group compared with 154 +/- 13.7 days in the control group) (p = 0.0001). The patients' compliance with the use of the device was excellent, and there were no serious complications related to its use. This study confirms earlier animal and clinical studies that demonstrated the efficacy of low-intensity ultrasound stimulation in the acceleration of the normal fracture-repair process.


How does pulsed low-intensity ultrasound enhance fracture healing?

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Pulsed low-energy ultrasound, a non-invasive therapeutic treatment modality, may improve callus formation and enhance fracture healing by initiating enhanced angioneogenesis.


Use of low-intensity pulsed ultrasound for posttraumatic nonunions of the tibia: a review of patients treated in the Netherlands.

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BACKGROUND: Low-intensity pulsed ultrasound is effective in fresh fracture healing, resulting in a 40% reduction in healing time. The aim of this study is to determine the effect of ultrasound treatment on established tibia nonunions. METHODS: The study group consists of all Dutch patients of posttraumatic consecutive nonunion of the tibia, who started their ultrasound treatment between January 2000 and February 2003. In total, 71 cases have been included, which involve 56 men and 15 women. Mean age was 40 years. Low-intensity pulsed ultrasound was the only new treatment. Strict criteria of enrollment minimized any spontaneous healing chance. According to literature, the spontaneous healing rate was between 5% and 30%. The study outcome, healed or failed, was the primary efficacy parameter. Thirty percent was chosen to represent the maximum expected spontaneous healing and was the basis for statistical evaluation. Stratification was performed for the variables at the ultrasound treatment start. RESULTS: The overall healing rate is 52 of 71 cases (73%). Ultrasound treatment shows a statistical significant higher healing rate compared with that of the spontaneous healing chance (p < 0.0001). Stratification shows no statistical significance for any of the variables analyzed. The long-term follow-up shows high compliance rate and no refractures. CONCLUSION: Tibia nonunions have a high occurrence rate and cause significant impairment to daily functioning. This study shows that low-intensity pulsed...
ultrasound is effective in the treatment of established tibia nonunions and can be seen as a good, safe, and cheaper alternative to surgery.


**Fracture repair with ultrasound: clinical and cell-based evaluation.**

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Fracture repair continues to be widely investigated, both within the clinical realm and at the fundamental research level, in part due to the fact that 5% to 10% of fractures result in either delayed union or nonunion, depending on the duration of incomplete healing. Beyond the temporal delay in repair, nonunions share the same unifying characteristic: all peristeal and endosteal repair processes have stopped and the fracture will not heal without surgical intervention. A less-invasive alternative method—low-intensity pulsed ultrasound—has shown promise as a treatment for delayed unions and nonunions and as a method to facilitate distraction osteogenesis. In this paper, we summarize the clinical effectiveness of low-intensity pulsed ultrasound with regard to fracture repair, treatment of nonunion, and distraction osteogenesis and we discuss the results of a multitude of published studies that have sought to elucidate the mechanisms behind that effectiveness through research on low-intensity pulsed ultrasound exposure on osteoblasts and osteoblast precursors. When evaluated clinically, low-intensity pulsed ultrasound was shown to enhance bone repair (most commonly noted as a decrease in healing time), although variations in patient population hindered a definitive claim to clinical effectiveness. In vitro cellular evaluation and in vivo studies on animal models have revealed an increase in cell proliferation, protein synthesis, collagen synthesis, membrane permeability, integrin expression, and increased cytosolic Ca(2+) levels as well as other increased indicators of bone repair in response to low-intensity pulsed ultrasound exposure. Many of the cellular responses to low-intensity pulsed ultrasound mirror the cellular responses to fluid-induced shear flow, suggesting a link between the two as one potential mechanism of action. The considerable amount of information that has been revealed about the behavior of osteoblasts under low-intensity pulsed ultrasound exposure suggests that the exact mechanism of action is complex. It is clear, however, that considerable progress is being made toward uncovering these mechanisms, which has served to encourage the use of low-intensity pulsed ultrasound in new applications. It is posited that successful noninvasive treatment strategies such as low-intensity pulsed ultrasound may be combined with other conventional and novel tissue-regeneration strategies to develop new treatments for large-scale bone defects.


**Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures.**

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BACKGROUND: Postoperative delayed union and nonunion is the most common complication in fracture treatment. Recent studies have shown an accelerating effect of low-intensity pulsed ultrasound (LIPUS) on fracture repair. However, the indications for delayed union and nonunion are not clear. To clarify the factors which influence the effects of LIPUS, the data from a previous prospective multicenter study on LIPUS treatment for postoperative delayed union and nonunion of long bone fractures were reanalyzed.
METHODS: Seventy-two cases of long bone fracture, including those of the femur, tibia, humerus, radius, and ulna, were analyzed. The mean time from the most recent operation to the beginning of LIPUS treatment was 11.5 (3-68) months. The relationship between the background factors and the union rate was analyzed using a logistic regression method. In addition, long bone fractures in an upper extremity or in a lower extremity were analyzed separately. RESULTS: The union rate was 75% in all the cases of long bone fracture. 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 in those that had long bone fracture of an upper extremity. There was also a significant relationship between the union rate and the time when a radiological improvement was first observed after the beginning of the treatment in all cases and in those with fractures in a lower extremity. When LIPUS treatment was started within 6 months of the most recent operation, 89.7% of all fractures healed. When an improvement in the radiological changes at the fracture site was observed after 4 months in those cases, then the sensitivity and specificity for union were more than 90%. CONCLUSIONS: LIPUS treatment should be started within 6 months of the most recent operation. Because LIPUS has been shown to be effective without causing either serious invasiveness or any undue risk to the patient, it may be considered the treatment of first choice for cases of postoperative delayed union or nonunion.


The effect of low-intensity pulsed ultrasound on callus maturation in tibial distraction osteogenesis.

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Callus distraction is currently the most popular method of bone lengthening. Prolonged treatment time is one of its major problems. In this study, we investigated the effect of low-intensity pulsed ultrasound on tibial distraction osteogenesis. We managed 20 patients with tibial defects ranging from 5 cm to 8 cm with distraction osteogenesis using the Ilizarov external fixator. After the completion of distraction, ten patients received daily 20 min of low-intensity pulsed ultrasound stimulation (30 mW/cm2) onto the bone lengthening site (group A) while rigid fixation was maintained in the remaining patients (group B). All patients were followed with weekly radiographs to determine the formation of an external cortex and an intramedullary canal, at which time the fixator was removed. The mean healing index in group A was 30 (27-36) days/cm while it was 48 (42-75) days/cm in group B. In group B, one patient failed to consolidate the regenerated bone. Low-intensity pulsed ultrasound stimulation is highly effective in achieving maturation of bone and reducing time of distraction osteogenesis.


Compound high-energy limb fractures with delayed union: our experience with adjuvant ultrasound stimulation (exogen).

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The use of low intensity pulsed ultrasound accelerates cortical and cancellous bone fracture healing. Seventeen patients with eighteen high-energy fractures of the long bones were treated with low intensity pulsed ultrasound supplementation to surgical skeletal stabilization and tissue flaps. Sixteen fractures were healed within 13-52 weeks after starting ultrasound supplementation despite severe soft-tissue
injuries and varying degrees of tissue loss. This method may be useful in the combined treatment of high-energy limb injuries.


**Comment in:**

**The effect of ultrasound on the healing of muscle-pediculated bone graft in scaphoid non-union.**

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The use of pedicled vascularised bone grafts from the distal radius makes it possible to transfer bone with a preserved circulation and viable osteoclasts and osteoblasts. Experiments performed at the basic science level has provided substantial evidence that low-intensity ultrasound can accelerate and augment the fracture healing process. Only an adequate double-blind trial comparing treatment by ultrasound stimulation in patients treated by similar surgical techniques can provide evidence of the true effect of ultrasound. This paper describes the results of such a trial. From 1999 to 2004, 21 fractures of the scaphoid with established non-union treated with vascularised pedicle bone graft were selected for inclusion in a double-blind trial. All patients were males, with an average age of 26.7 years (range 17-42 years) and an average interval between injury and surgery of 38.4 months (range 3 months-10 years). Low-intensity ultrasound was delivered using a TheraMed 101-B bone-growth stimulator (30 mW/cm², 20 min/day), which was modified to accomplish double-blinding. These modifications did not affect the designated active units. The placebo units were adjusted to give no ultrasound signal output across the transducer. Externally, all units appeared identical but were marked with individual code numbers. Patients were randomly allocated to either an active or placebo stimulation. Follow-up averaged 2.3 years (range 1-4 years). All patients achieved fracture union (active and placebo groups), but compared with the placebo device (11 patients), the active device (ten patients) accelerated healing by 38 days (56 +/- 3.2 days compared with 94 +/- 4.8 days, p<0.0001, analysis of variance).


**Management of non-union with pulsed low-intensity ultrasound therapy--international results.**

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In prospective, randomized, double-blind, placebo-controlled, multi-center clinical studies, pulsed, low-intensity ultrasound has been proven to be effective in decreasing the time to heal in both fresh diaphyseal (tibia) and metaphyseal (distal radius) fractures. It also decreases the likelihood of a delayed union (>150 days to heal) in tibia fractures and loss of reduction in distal radius fractures. World-wide clinical studies, using pulsed, low-intensity ultrasound for treatment of non-union in a self-paired control study design, have demonstrated a heal rate of 88% with an average treatment time of 4.5 months in non-unions and an average fracture age of 23 months. The therapy is safe and non-invasive, and is used by the patient at home for a 20-minute treatment session per day.


**Low-intensity pulsed ultrasound for the treatment of bone delayed union or nonunion: a review.**
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.


**Low-intensity ultrasound enhances maturation of callus after segmental transport.**

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The purpose of this study was to determine whether low-intensity ultrasound can be used to enhance callus maturation. Fifteen-millimeter bone defects at the metatarsal bones of sheep were treated with a segmental bone transport for 16 days. The callus formations in the bone defects were allowed to mature for 63 days before the animals were sacrificed. Eighteen sheep were operated on and divided into two groups. One group was treated with low-intensity ultrasound for 20 minutes per day, whereas the other group served as an untreated control group. Biomechanical tests after removal of the metatarsals showed significantly higher axial compression stiffness and significantly higher indentation stiffness of callus tissue in the healing zone in the group treated with ultrasound. Also, histologic analysis of the cortical defect zone showed significantly more callus formation and more active zones of endochondral ossification in the group treated with ultrasound. Stimulation of callus maturation by ultrasound is possible, similar to stimulation of fresh fracture healing, and may be used to shorten clinical treatment times.


**[Application of low intensity, pulsed ultrasound on distraction osteogenesis of the humerus. Case report]**

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Low intensity pulsed ultrasound accelerates fracture healing both clinically and experimentally. Based on recently published animal studies, an improvement in regenerative bone maturation after distraction osteogenesis due to low intensity, pulsed ultrasound is also expected. We report on an 18 year-old female patient suffering from an acquired shortening of the right upper arm of 10 cm after humeral osteitis as a baby. The patient was admitted to hospital for corticotomy and distraction osteogenesis at the afflicted humerus. Due to the published experimental results in animals which indicate an
improvement in bone regeneration during callotasis with the additional application of low intensity, pulsed ultrasound, we decided to try this procedure. The calculated distraction consolidation index was 21 days/cm, which is below the mean of 30 days/cm reported in the literature for humeral lengthening by distraction osteogenesis. The calculated healing index according to Paley was 0.7 months/cm in our patient. Compared to reference data, in which a range of from 0.87 months/cm to 1.5 months/cm is reported, our patient showed an accelerated maturation of distraction callus. The duration of treatment of the patient was clearly shortened by the additional application of low intensity, pulsed ultrasound. If distraction osteogenesis is correctly indicated, the early use of low intensity, pulsed ultrasound should be considered, since an acceleration of callus formation with consecutive shortening of treatment time could be attained while wearing an external fixator, leading to a decrease in cumulative complications, such as pin tract infections. Further studies from our research group regarding this topic will follow.


Low-intensity pulsed ultrasound accelerates maturation of callus in patients treated with opening-wedge high tibial osteotomy by hemicallotasis.

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BACKGROUND: Opening-wedge high tibial osteotomy by hemicallotasis for osteoarthritis in the medial compartment of the knee requires external fixation for a long time, until callus maturation is complete. The aim of this study was to determine if low-intensity pulsed ultrasound would accelerate callus maturation when applied after distraction to limbs treated with opening-wedge high tibial osteotomy by hemicallotasis.

METHODS: Twenty-one patients with symmetric grades of osteoarthritis and similar degrees of varus deformity in the two knees underwent bilateral one-stage opening-wedge high tibial osteotomy by hemicallotasis. After completion of distraction, the bone mineral density of the distraction callus was measured. Then, one randomly selected limb was subjected to ultrasound treatment for twenty minutes daily until removal of the external fixator. The contralateral limb was left untreated to serve as the control. After four weeks of treatment, bone mineral density was measured again.

RESULTS: During the four-week treatment period, the mean increase in callus bone mineral density was significantly greater in the ultrasound-treated tibiae (0.20 +/- 0.12 g/cm(2)) than in the control tibiae (0.13 +/- 0.10 g/cm(2)) (p = 0.02, unpaired t test). In eighteen patients the increase in the bone mineral density was greater in the ultrasound-treated limb than in the control limb, whereas in three patients the increase was greater in the control limb.

CONCLUSIONS: We found that low-intensity pulsed ultrasound applied during the consolidation phase of distraction osteogenesis accelerates callus maturation after opening-wedge high tibial osteotomy by hemicallotasis in elderly patients.


[Is low intensity ultrasound effective in treatment of disorders of fracture healing?]

[Article in German]
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This prospective consecutive study judges the effectiveness of pulsed low-intensity ultrasound for treatment of boney healing disorders. 86 out of 100 treatments were successful. Although in these 100 cases 64 delayed unions and 36 nonunions were enrolled ultrasound therapy was performed as an
alternative to the indicated operation in every case. Excluding ten cases of ununited fractures of the scaphoid no additional therapy was performed in any case. Stratifying the data no significant differences in healing rate and treatment time were observed between delayed unions and non-unions and between atrophic and hypertrophic healing disorders. Judging the healing rate of 86% one has to take into consideration that according to our in- and excluding criteria we had a preselected sample of patients. Nevertheless the effectiveness of pulsed low-intensity ultrasound for treatment of disorders of the fracture repair process is evident.


Low intensity ultrasound treatment increases strength in a rat femoral fracture model.

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Bilateral closed femoral shaft fractures were made in 22 male Long-Evans rats. In 16 animals, ultrasound was applied to one limb for 15 minutes daily 10 times within the first 14 postoperative days. The treated limbs received a 200 microseconds burst of 1.5 or 0.5 MHz sine waves repeated at 1.0 kHz at a spatial average and temporal average intensity of 30 mW/cm2. The contralateral limb of each animal served as a nontreated control. Six remaining animals with fractures and six additional animals without fractures received sham ultrasound treatment to control for the effects of anesthesia and handling. Fracture repair was evaluated on postoperative day 21 by radiography, mechanical testing in torsion, and histology. Five of 16 ultrasound-treated fractures showed obliteration of the fracture gap on radiographs, whereas none of the 28 controls did. The average maximum torque of fractures treated with either signal was 22% greater than that of the contralateral controls (p < 0.05). The stiffness of treated fractures was greater than that of control fractures, but the difference was significant only in animals treated with the 1.5 MHz signal (p < 0.02). Sham treatment did not affect repair in the control group. These results indicate that low-intensity pulsed ultrasound at either 0.5 or 1.5 MHz can accelerate fracture repair at 21 days in this highly controlled model.


Low intensity pulsed ultrasound increases the matrix hardness of the healing tissues at bone-tendon insertion-a partial patellectomy model in rabbits.

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BACKGROUND: This study evaluated the low intensity pulsed ultrasound enhancement on matrix hardness of the healing tissues at the bone-tendon junction. METHODS: Sixteen 18 week-old mature female rabbits were used. An established transverse partial patellectomy was performed at the distal one-third of the patella. Animals were then divided according to their body weight into ultrasound group (n = 8) with daily treatment of low intensity pulsed ultrasound and control group (n = 8) without ultrasound treatment. Animals were euthanized at week 8 and 16 postoperatively to evaluate the radiographic new bone formation and the Vickers hardness of the matrix of the healing tissues at the bone-tendon junction. FINDINGS: (1) Comparing with the control group, the anterior-posterior area of the new bone in the ultrasound treated group was found on average to be 3.0 and 3.1 times greater at week 8 and 16, respectively (P < 0.01). (2) The Vickers hardness of the new bone in ultrasound group was 11.3% (P < 0.05) significantly lower at week 8 but 20.0% (P < 0.05) significantly higher at week 16.
as compared with that of the control group. (3) The Vickers hardness of the newly regenerated fibrocartilage zone, healing tendon, and cartilaginous metaplasia in ultrasound group was found higher than the control group at both week 8 and 16, but the difference was significant at week 16 only, being 44.1% (P < 0.05), 20.1% (P < 0.01), and 46.4% (P < 0.01) higher, respectively. INTERPRETATION: The preliminary findings suggested for the first time that low intensity pulsed ultrasound treatment resulted in the enhancement of the matrix hardness in new bone, fibrocartilage, cartilaginous metaplasia, and healing tendon at the healing bone-tendon junction. These findings can be extrapolated into clinical practice, i.e. the more rapid healing induced by low intensity pulsed ultrasound, the earlier mobilization of the affected joint. The beneficial effects on prevention of the musculoskeletal deterioration resulting from the prolonged immobilization would be therefore expected.


Non-invasive low-intensity pulsed ultrasound accelerates bone healing in the rabbit.

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The effect of ultrasound (US) on the rate of fibula osteotomy healing in 139 mature New Zealand white rabbits was assessed in this study. Bilateral midshaft fibular osteotomies were made using a 1-mm Gigli saw. US was noninvasively applied to one limb for 20 minutes daily, while the contralateral limb served as a control. A 2.5-cm PZT transducer was applied to both limbs, with the treated limb receiving a 200-microseconds burst of 1.5-MHz sine waves repeated at 1.0 kHz. The incident intensity was approximately 30 mW/cm2. Animals were killed at intervals between 14 and 28 days. Maximum strength increases (significant to p less than or equal to 0.01) ranged from 40 to 85% from postoperative day 14 to 23. On day 28, no significant difference in ultimate strength was noted. From day 17 through day 28, all US-treated fractures were as strong as intact bones (p less than or equal to 0.005). On the other hand, the ultimate strength of the control osteotomies attained intact values only by day 28. These results indicate that biomechanical healing is accelerated by a factor of nearly 1.7. This occurs with an overall acceleration of the healing curve in this fresh fracture model. If noninvasive low-intensity pulsed sine wave ultrasound can significantly accelerate bone repair in clinical application with an in-home treatment of 20 minutes daily, then US may be a useful adjunct for fracture care with a concomitant impact on patient morbidity.


The effect of fracture and fracture fixation on ultrasonic velocity and attenuation.

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Measurement of the velocity of propagation and attenuation of ultrasound (200 kHz) is believed to be a useful non-invasive technique for assessing the mechanical properties of bone. A new method for the determination of ultrasound velocity and attenuation of longitudinal waves in cortical bone was used in vivo and in situ on intact and fractured human tibiae. The measured ultrasound attenuation and velocity were found to be unaffected by the soft tissue between transducers and bone. The ultrasound velocity in vivo on control tibiae was 3614 +/- 32 m s⁻¹ and the attenuation was 5.52 +/- 0.43 dB MHz⁻¹ cm⁻¹. The ultrasound velocity in fractured tibiae was considerably lower 1 week after fracture (2375 +/- 82 m s⁻¹), but had significantly increased after 3 weeks (to 2882 +/- 90 m s⁻¹). A higher attenuation was measured 1 week after fracture (17.81 +/- 3.91 dB MHz⁻¹ cm⁻¹), but it had decreased again 3 weeks after fracture
(10.42 +/- 3.56 dB MHz-1 cm-1). In situ studies under well-defined conditions confirmed the in vivo results. The effects of internal plate fixation and gradually cutting through the cortex on the ultrasound velocity and attenuation were studied in situ. These results demonstrate the clinical potential of this technique for the non-invasive assessment of bone fracture healing.

**J Trauma. 2008 Dec;65(6):1446-52.**

**The role of low intensity pulsed ultrasound therapy in the management of acute fractures: a systematic review.**

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BACKGROUND: The aim of this study was to review the evidence regarding the use of low intensity pulsed ultrasound (LIPUS) in the management of acute long bone fractures. METHODS: Systematic review of Medline, Embase, and CINAHL databases. Further published studies were retrieved by hand searching bibliographies of relevant articles. Retrieved studies were limited to English-language studies published since 1956. Retrieved studies were excluded from review using the following criteria: case reports, exclusively pathologic fractures, treatment of therapeutic osteotomies and arthrodesis, initiation of ultrasound therapy after the first month following injury, no reporting of assessment of time to fracture healing, cellular studies, and nonclinical articles. Studies were reviewed independently by two reviewers using the CONSORT score. No statistical analysis was performed as the data from the studies were not suitable for pooled analysis. RESULTS: Seven randomized controlled trials and two meta-analyses were retrieved using the search strategy. CONCLUSION: The literature supports the use of LIPUS in the treatment of acute fractures treated with plaster immobilization.

**Comment in:**

**Diagnostic ultrasound treatment increases the bone fracture-healing rate in an internally fixed rat femoral osteotomy model.**

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OBJECTIVE: To investigate the healing effects of diagnostic ultrasound in a standardized rat femur fracture model. METHODS: Thirty-two male rats aged 14 weeks were used, and each rat's right femur was osteotomized and stabilized under anesthesia. The rats were then divided into 4 groups. Five days after surgery, ultrasound was applied every fifth day with diagnostic sonographic equipment and a probe with a 7.5-MHz frequency and 11.8-mW/cm² total output intensity for 10 minutes in each session. Ultrasound was applied 8 times in group A, 3 times in group B, and only once in group C. Ultrasound was not applied to sham-operated group D. Healing and callus formation of the rats’ femur fractures were evaluated by radiography and dual-energy x-ray absorptiometry. RESULTS: Dual-energy x-ray absorptiometric and radiographic results showed that the ultrasound therapy accelerated the fracture healing. Radiographically, groups A and B showed better fracture healing than groups C and D. Ultrasound exposure increased both the whole-bone mineral density and the density at the fracture region, increasing in parallel with the exposure period. CONCLUSIONS: This study confirms the previously shown efficacy of low-intensity ultrasonic stimulation in acceleration of the normal fracture repair process even when performed with a diagnostic sonographic device.

**Foot Ankle Int. 2008 Oct;29(10):970-7.**
The evaluation of the healing rate of subtalar arthrodeses, part 2: the effect of low-intensity ultrasound stimulation.

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BACKGROUND: Arthrodeses of hindfoot joints is commonly used to treat a multitude of painful conditions and deformity. Use of adjuvant low-intensity ultrasound bone stimulation has demonstrated promising results in the treatment of acute fractures and fracture nonunions. The purpose of this 12-month prospective study was to evaluate the healing rate and clinical results of patients undergoing primary subtalar arthrodeses with adjuvant low-intensity ultrasound bone stimulation. MATERIALS AND METHODS: Fifteen consecutive patients participated in the study. Routine radiographs and CT scans were obtained, and clinical outcomes gathered. The clinical and radiographic data were compared to a similar cohort of patients previously reported on that had not received ultrasound bone stimulation. RESULTS: The patients who received ultrasound bone stimulation showed a statistically significant faster healing rate on plain radiographs at 9 weeks (p = 0.034) and CT scan at 12 weeks (p = 0.017). A 100% fusion rate was noted. The American Orthopaedic Foot and Ankle Society (AOFAS) ankle and hindfoot score was also improved at 12 months postoperatively, a finding that was statistically significant (p = 0.026). CONCLUSION: This is the first paper, to our knowledge, to prospectively evaluate ultrasound bone stimulation in primary hindfoot arthrodesis patients. We were able to show significantly improved radiographic as well as clinical outcomes compared with a similar cohort of patients who did not receive adjuvant ultrasound stimulation. We believe that low-intensity ultrasound bone stimulation is indicated in primary hindfoot fusions, particularly in those patients at higher risk for nonunion.


Low-intensity pulsed ultrasound in the conservative treatment of pseudoarthrosis.

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AIM: The management of pseudarthrosis remains a challenge. Several in vivo animal and controlled clinical studies have demonstrated that low-intensity pulsed ultrasound can influence fracture healing. METHODS: A prospective longitudinal design was used. Fifteen patients (12 males and 3 females; mean age 35.5+/-12.9, range 18 to 60), all amateur athletes, under treatment for pseudarthrosis at different sites (average fracture age: of 336.6+/-60.1 days) were treated with a single 20 min daily application of low-intensity pulsed ultrasound (frequency 1.5 MHz and intensity 30 mW/cm2). All patients underwent clinical examination and plain radiography at the beginning of treatment and were followed up clinically and radiographically at 4, 8, 12, 16, 20 and 24 weeks until the fracture healed. RESULTS: All fractures healed with a mean healing time of 94.7+/-43.8 days. CONCLUSION: Low-intensity pulsed ultrasound is effective in the management of long standing fracture non-unions. Prospective randomized studies are needed to confirm the value of this modality of treatment.


Transosseous application of low-intensity ultrasound for the enhancement and monitoring of fracture healing process in a sheep osteotomy model.

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The purpose of this study is twofold: (a) to investigate the application of transosseous low-intensity pulsed ultrasound (LiUS) on the enhancement of fracture healing and (b) to demonstrate the ability of transosseous ultrasound propagation to monitor the healing process. A midshaft tibial osteotomy model was used on 40 skeletally mature sheep, and an external fixator was applied to maintain the reduction and stabilization of the osteotomy. Two ultrasound transducers were implanted into the fracture site in contact with the bone. For investigating the efficacy of LiUS, the animals were randomly divided in two equal groups: the treatment group and the control group. The LiUS-treated animals received 200-micros bursts of 1-MHz sine waves with a pulse repetition rate of 1 kHz and average intensity of 30 mW/cm2, for 20 min daily. For monitoring purposes, an ultrasound dataset was constructed consisting of serial ultrasound measurements obtained from healing bones. Animals' sacrifice took place on the 100th post-operative day. The effect of LiUS on fracture healing was evaluated using radiographs, destructive three-point bending testing and quantitative CT-based bone mineral density (BMD) measurements. Survival analysis using Kaplan-Meier curves showed significantly higher probability of radiographic healing for the animals in the treatment group (P = 0.009). Statistical significance was also observed for callus BMD (P = 0.003, Wilcoxon nonparametric test), the breaking load (P = 0.001), extrinsic stiffness (P = 0.019), Young's modulus (P = 0.043) and ultimate strength (P = 0.051) in favor of the LiUS-treated limbs. Analysis of the obtained ultrasonic measurements showed that the propagation velocity across healing bones constitutes a significant feature able to early distinguish between healed and nonhealed bones (area under ROC curve was 0.810 and 0.841 on the 80th and 100th post-operative days, respectively). Both the LiUS application and the ultrasonic measurements are supported by an integrated telemedicine system which also incorporates an ultrasound wearable device and a patient management system.


Lack of efficacy of low-intensity pulsed ultrasound on prevention of postmenopausal bone loss evaluated at the distal radius in older Chinese women.

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A within-subject, randomized, and prospective intervention trial was done to evaluate the potential effect of low-intensity pulsed ultrasound on prevention of postmenopausal bone loss. Twenty healthy postmenopausal women between the ages of 51-81 years met the inclusion criteria. The treatment hand was randomly selected, and the contralateral site served as a control. Integral and trabecular bone mineral density were measured using highly precise multilayer peripheral quantitative computed tomography at the bilateral distal radius at baseline, 3 months after daily low-intensity pulsed ultrasound treatment, and 3 months after discontinuing treatment. Results showed that the rate of bone change (trabecular bone mineral density and integral bone mineral density) did not significantly differ between the site treated with low-intensity pulsed ultrasound and the contralateral control at either followup. Also, during the followup, bone mineral density did not change significantly in the contralateral control site. This was the first prospective and randomized study to show that low-intensity pulsed ultrasound at the current regime did not have significant effects on intact bone for prevention of postmenopausal bone loss in the distal radii of older Chinese women.


Low-intensity transosseous ultrasound accelerates osteotomy healing in a sheep fracture model.
BACKGROUND: Low-intensity transcutaneous ultrasound can accelerate and augment the fracture-healing process. The aim of this study was to investigate the effect of transosseous application of low-intensity ultrasound on fracture-healing in an animal model. METHODS: A midshaft osteotomy of the left tibia was performed in forty sheep. An external fixator was used to stabilize the osteotomy site. A thin stainless-steel pin was inserted into the bone, 1.0 cm proximal to the osteotomy site. Ultrasound was transmitted through the free end of this pin, with a PZT-4D transducer. In twenty animals, the treated limb received a 200-microsec burst of 1-MHz sine waves repeated at 1 kHz with an average intensity of 30 mW/cm(2) for twenty minutes daily. Twenty other animals underwent the same surgery but did not receive the ultrasound (controls). Animals were killed at seventy-five and 120 days postoperatively. Radiographic evaluation was performed every fifteen days. Mechanical testing and quantitative computed tomography were performed after death. RESULTS: Fractures treated with ultrasound healed significantly more rapidly, as assessed radiographically, than did the controls (seventy-nine compared with 103 days, p = 0.027). On day 75, the mean cortical bone mineral density (and standard deviation) was 781 +/- 52 mg/mL in the treated limbs compared with 543 +/- 44 mg/mL in the control group (p = 0.014), and the average ultimate strength (as assessed with a lateral bending test) was 1928 +/- 167 N in the treated limbs compared with 1493 +/- 112 N in the control group (p = 0.012). No significant differences were noted on day 120. CONCLUSIONS: This study demonstrated that low-intensity transosseous ultrasound can significantly accelerate the fracture-healing process, increase the cortical bone mineral density, and improve lateral bending strength of the healing fracture in a sheep osteotomy model.


Low-intensity pulsed ultrasound initiates bone healing in rat nonunion fracture model.

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Low-intensity pulsed ultrasound exposure has been shown clinically to shorten the fracture repair process and to induce healing of nonunions in humans, but its mechanism of action remains unclear. In this study we investigated the effect and mechanism of low-intensity pulsed ultrasound on nonunion fracture healing in rat tibias. A consistently reproducible nonunion was produced in rat tibias by muscle interposition without osteotomy. This model was produced by creating a closed tibial fracture with only the distal end of the tibialis anterior muscle interposed into the fracture site. One limb was noninvasively exposed to low-intensity pulsed ultrasound (a 200-millisecond burst of sine waves of 1.5 MHz, repeating at 1.0 kHz) for 20 minutes daily. The incident intensity was approximately 30 mW/cm2. Rats were killed at intervals between 2 and 6 weeks. The events were assessed by radiographs, microfocus X-ray computed tomograms, and histologic examination. After 6 weeks of exposure, 7 of 14 nonunion fractures showed healing on radiologic assessment. The results of three-dimensional microfocus X-ray computed tomographic reconstruction and histologic examination also supported this finding. On the other hand, all control tibias remained in a state of nonunion during the same period. These results indicate that low-intensity pulsed ultrasound promotes healing in the rat nonunion fracture model.


Effect of low-intensity ultrasound stimulation on consolidation of the regenerate zone in a rat model of distraction osteogenesis.

Eberson CP, Hogan KA, Moore DC, Ehrlich MG.
This study was performed to explore the tissue-level changes in mineralization caused by low-intensity ultrasound stimulation after distraction osteogenesis. Unilateral femoral lengthenings (7 mm) were performed on 34 male Sprague-Dawley rats. Half of the animals received daily ultrasound stimulation for 5 weeks; the remaining animals received sham treatments. Healing was assessed with serial radiographs, quantitative micro-computed tomography, and biomechanical testing. Twenty-one animals were evaluated at the conclusion of the study (9 experimental, 12 control). Radiographically, healing of the ultrasound-treated bones preceded that of the sham-treated bones by approximately 1 week. Bone volume fraction and trabecular bone pattern factor were significantly higher in the ultrasound-treated animals, but there were no significant differences in bone mineral content or bone mineral density. The ultrasound-treated femurs were 20% stiffer and 33% stronger than the control femurs, but the differences were not statistically significant. These findings suggest that pulsed, low-intensity ultrasound matures the regenerate by altering the microarchitecture of the newly formed bone.

Stimulation of fracture healing in a canine ulna full-defect model by low-intensity pulsed ultrasound.

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Because no report has been issued on the healing effects of low-intensity pulsed ultrasound on moderate to large fracture gaps, we performed an experimental study using a canine ulna full-defect model. Ten mongrel male dogs were divided into two groups: a small defect group and large defect group. The defects were made on the middle one third of both ulnae and one side only was randomly selected for ultrasound sonication, at 1 MHz, 200 microsecond bursting sine wave in 50 mW/cm² spacial average and temporal average. Sonication was started on the day after surgery and applied for 15 minutes once a day for six days a week. In the small defect group, the means of the radiologic scores, as described by Lane and Sandhu, were 0.6, 4.4, and 8.4 in the control side and 1.8, 6.0, and 10.4 in the treatment side one, three, and five months after the operation, respectively (p=0.0372). In the large defect model, the corresponding means were 2.2, 3.4, and 6.0 in the control side and 3.3, 5.4, and 9.2 in the treatment side (p= 0.009). Low-intensity pulsed ultrasound enhanced new bone formation in small and large full-defects and decreased the incidence of nonunion in the large defect model.

The action of low-intensity pulsed ultrasound in bones of osteopenic rats.

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In this study, the action of low-intensity pulsed ultrasound for 20 min/day, during twenty days, was analyzed in an attempt to revert bone loss in the proximal femur of osteopenic rats. Although the quantitative results of bone mineral content (BMC) demonstrated no significant difference among the groups (P > 0.05), the histologic investigations have shown the occurrence of recent bone formation not observed in the nontreated group. Moreover, the treated femur presented less microarchitectural
deterioration than the nontreated group. These results suggest that the low-intensity ultrasound can interfere in a positive way on osteoporosis.

**ULTRASONIC THERAPY FOR THE PREVENTION AND CORRECTION OF CONTRACTURES AND BONE MINERAL LOSS ASSOCIATED WITH WING BANDAGING IN THE DOMESTIC PIGEON (COLUMBA LIVIA)**

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**Abstract**

Figure-of-eight wing bandaging is widely used to treat wing injuries, to immobilize wings before and after fracture repair, and during transient wing paralysis. However, prolonged bandaging can lead to bone loss and to contractures and reduced range of joint motion. Studies evaluating the efficacy of therapeutic ultrasound to reverse and prevent bandaging-associated contractures in pigeons (Columba livia) showed a significant increase in elbow and carpal extension after 10 twice weekly ultrasound treatments when started either 4 or 11 days after bandage placement. In addition, after 42 days of wing bandaging, three ultrasound treatments stimulated a faster reversal of carpal wing rotation loss than removal of the bandage over the 10-day treatment period. Finally, bone loss in response to 28 days of bandaging was significant, progressed at 2.8% per week, and was not affected by ultrasound treatment twice weekly during this period. Therefore, therapeutic ultrasound prevented and reversed loss of wing extension associated with figure-of-eight bandaging but did not lessen the disuse osteoporosis created by bandaging in these birds.

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**Efficacy of pulsed low-intensity ultrasound in wound healing: a single-case design.**

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Therapeutic ultrasound is used clinically to enhance healing of pressure ulcers. Limited clinical research is available and no consensus exists regarding the efficacy of ultrasound for treating pressure ulcers, particularly full-thickness pressure ulcers, in the elderly. To assess the efficacy of pulsed low-intensity ultrasound on wound healing, a double-blind, single-case, baseline-AB study was conducted. The participant, a patient in a skilled nursing facility, was a 75-year-old woman with a Stage III pressure ulcer over the coccyx. Pulsed low-intensity ultrasound was compared to placebo ultrasound. After the 1-week baseline period, each ultrasound treatment was administered 5 days a week for two consecutive weeks. Throughout the baseline and ultrasound treatment periods, the patient additionally received the standard wound care treatment program at the facility. The rate of wound surface area reduction was used as the measure of wound healing. Healing was significantly faster ($P = 0.001$) during the pulsed low-intensity ultrasound period (34.0 mm$^2$/day) compared to the placebo ultrasound period (12.6 mm$^2$/day), but was significantly faster ($P = 0.001$) during the baseline period (50.8 mm$^2$/day) compared to the pulsed low-intensity ultrasound period. Healing in this patient was faster than rates noted in the literature under similar conditions. The precise effect of either ultrasound intervention in this study could not be determined. Neither pulsed low-intensity ultrasound nor placebo ultrasound likely had an appreciable effect on healing of this patient's pressure ulcer beyond that of the standard-care protocol.