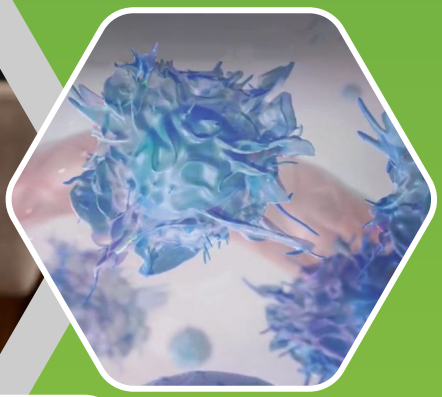
AccelStim™
Bone Healing Therapy

How LIPUS Works

Low-Intensity Pulsed Ultrasound



ORTHOFIX®

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How LIPUS Affects Fracture Healing

The fracture repair process is divided into four stages: inflammation, soft callus formation, hard callus formation, and bone remodeling.[1] Low-intensity pulsed ultrasound treatment (LIPUS) has been shown to accelerate fracture healing at every stage, with maximum benefit achieved when applied throughout the entire healing process.[1]

The Orthofix AccelStim™ device uses a low-intensity pulsed ultrasound mechanical pressure wave composed of 1000 pulses per second to stimulate a response at the cellular level.[2,3] After contacting bone, the mechanical pressure wave creates nanomotion at the fracture site producing a reaction at the cellular level.[2,3]

The Orthofix AccelStim device helps promote bone healing by providing non-invasive therapy for healing nonunion fractures and accelerating the time to healing of fresh fractures.[4]

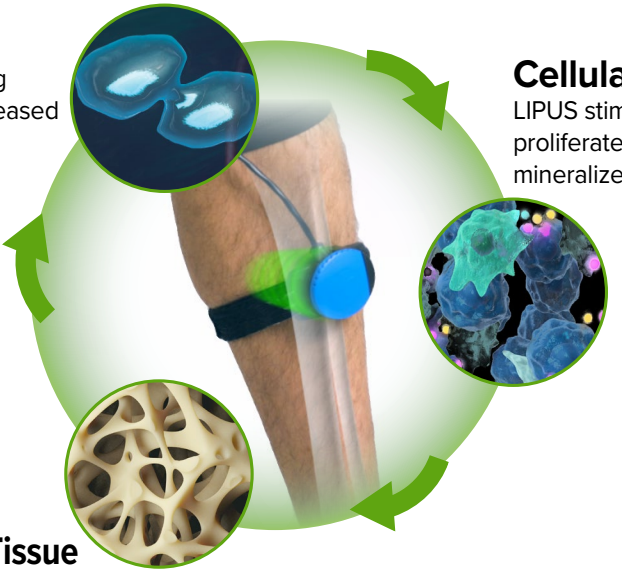
The Orthofix AccelStim device uses a unique LIPUS signal to amplify your body's natural bone repair processes.[4]

LIPUS Amplifies Bone Healing

LIPUS works by sending ultrasound waves through the skin and surrounding soft tissue to reach the site of the bone fracture.[5,6] This stimulates signaling pathways,[7] which in turn promotes mesenchymal stem cells to migrate towards the site of the fracture.[8] The ultrasound waves activate certain cell receptors,[9] setting off a series of reactions, referred to as a cascade.

One result of this event is that stem cells begin to proliferate, differentiate, and mineralize to form new bone.[8,10] LIPUS increases upregulation of the processes critical to bone repair, thus increasing new bone formation.[5,11]

Molecular
LIPUS stimulates signaling pathways, leading to increased cell differentiation.[1,12]



Cellular
LIPUS stimulates bone cells to proliferate, differentiate, and mineralize.[18]

Tissue
LIPUS increases new bone formation.[25]

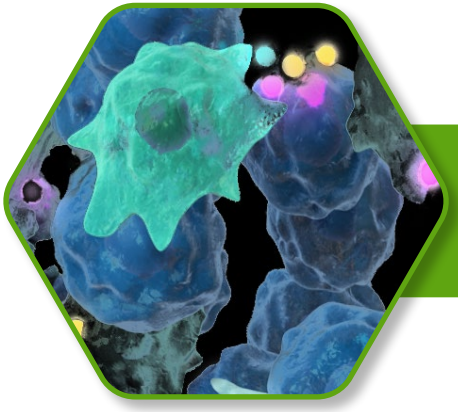
The Orthofix AccelStim device helps promote bone healing by providing noninvasive LIPUS therapy for healing nonunions and accelerating time to healing of indicated fresh fractures.[4]

LIPUS at the Molecular Level

LIPUS stimulates signaling pathways, leading to increased cell differentiation.

- LIPUS stimulates the expression of aggrecan in chondrocytes,[12,13] leading to accelerated cartilage formation, which is part of the initial phase of the fracture healing process.[1]
  - LIPUS increases aggrecan expression 10-20% as shown by immunohistochemical staining of chick embryos.[13]
- LIPUS stimulates integrin, a transmembrane cell receptor, leading to increased gene expression of osteogenic growth factors and markers of osteogenesis.[7,14] These include osteonectin, osteopontin, and insulin growth factor-1 (IGF-1).[15]
  - Staining by immunofluorescence showed a significant increase in integrin after 15 minutes of LIPUS exposure in rabbit synovial cells.[7]
- LIPUS stimulation alters the gene expression profile in osteocytes thus modifying the function of osteogenic and inflammatory cells that are involved in the fracture healing process.[16,17]
  - LIPUS stimulates an anabolic response in osteocytes.[17]

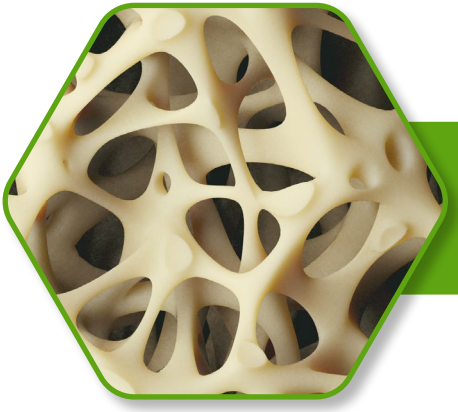
LIPUS at the Cellular Level



LIPUS stimulates bone cells to proliferate, differentiate, and mineralize.

- LIPUS stimulates undifferentiated mesenchymal stem cells to differentiate into osteoblasts.[8,18]
  - After 13 days of differentiation, mesenchymal stem cells treated with LIPUS were 10% more differentiated than the control group.[19]
- In response to LIPUS, periosteal cells and osteoblastic cells increase expression of osteocalcin, alkaline phosphatase, and Vascular Endothelial Growth Factor (VEGF). These result in an increase in mineralization and enhanced angiogenesis.[20,21]
  - Periosteal cell showed significantly more mineralization after four days of LIPUS treatment when compared to the control group.[20]
- Enhanced stimulation of osteogenic cells by LIPUS drive endochondral ossification.[10,20]
  - LIPUS treatment for 16 days accelerated endochondral ossification in mice, shown by histology.[22]

LIPUS at the Tissue Level

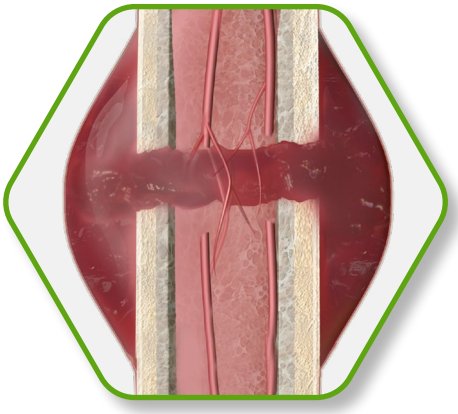


LIPUS increases new bone formation.

- LIPUS increases mineralization and calcium deposition.[23,24]
  - The volume and amount of new bone formation was greater in the LIPUS group than the control, shown by micro-CT.[24]
- LIPUS enhances bone formation.[25,26]
  - Bone formation in the LIPUS treated group started earlier and became more extensive than bone formation in the control group.[26]
- LIPUS improves osteogenic differentiation, mineralization, volume of newly formed bone, and osseointegration.[11,27]
  - The LIPUS treated group showed 86% spinal fusion in a rabbit model, compared to 14% in the control group.[27]
- LIPUS accelerates all stages of the fracture repair process (inflammation, bone formation, and bone remodeling), by increasing mineralization and reducing the inflammatory response.[1,22]
  - Early endochondral ossification in the LIPUS treated femur was greater than in the control, shown by histology and micro-CT, confirming a significant increase in newly formed bone.[1, 22]

Four Phases of Bone Healing

Phase 1: Inflammation

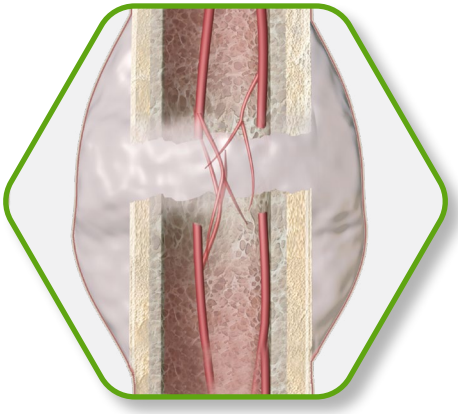


- When a bone breaks, blood vessels in the bone and periosteum are torn and hemorrhage, and a hematoma (blood clot) forms at the fracture site.
- Blood comes from blood vessels, marrow, and surrounding tissues, forming a hematoma that aids in cell recruitment to the fracture site.[5]

LIPUS Benefit

- LIPUS stimulates ultrasound waves through skin and surrounding soft tissue to reach the site of the bone fracture.[20,28]
- LIPUS activates anti-inflammatory response by upregulating the anti-inflammatory gene expression.[20,28]

Phase 2: Formation of Soft Callus

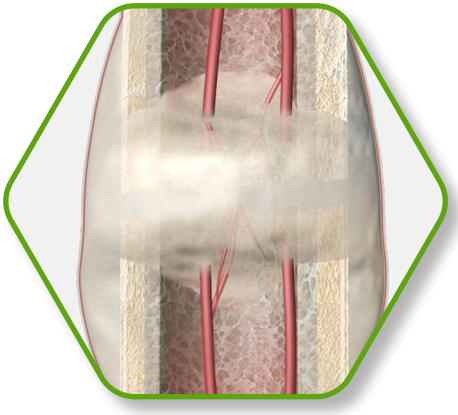


- New blood vessel formation occurs, which is called angiogenesis.[5]
- The major growth factor responsible for angiogenesis is VEGF. VEGF is produced by osteoblasts and periosteal cells.[5]
- Proliferation and osteoblastic differentiation of mesenchymal stem cells takes place to form the soft callus.[5]

LIPUS Benefit

- LIPUS helps to increase the formation of new blood vessels at the fracture site.[29]
- LIPUS treatment enhances the TGFB-triggered differentiation of chondrocytes in culture and accelerates the formation of extracellular matrix.[30]

Phase 3: Formation of Hard Callus

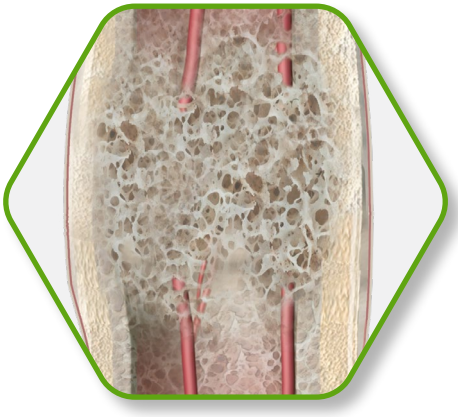


- Calcium is deposited in the new bone structure in a process called ossification. The hard callus continues to grow, bridging the gap in the broken bone until the two ends meet.[31,32]

LIPUS Benefit

- LIPUS treatment increases soft tissue mineralization to stabilize the fracture by adding a rigid structure and strength.[31,32]
- LIPUS activates anti-inflammatory response by upregulating the anti-inflammatory gene expression.[20,2.]

Phase 4: Bone Remodeling



- Mineralized callus is the outer layer of bone tissue that normally forms like scar tissue at the ends of a broken bone once it has healed.[33]
- Eventually, the fracture callus is remodeled into a new shape which closely duplicates the bone's original shape and strength.[33]

LIPUS Benefit

- LIPUS accelerates both the normal formation (remodeling) and recycling (resorption) of bone tissue, for a faster formation of the mineralized callus.[33]

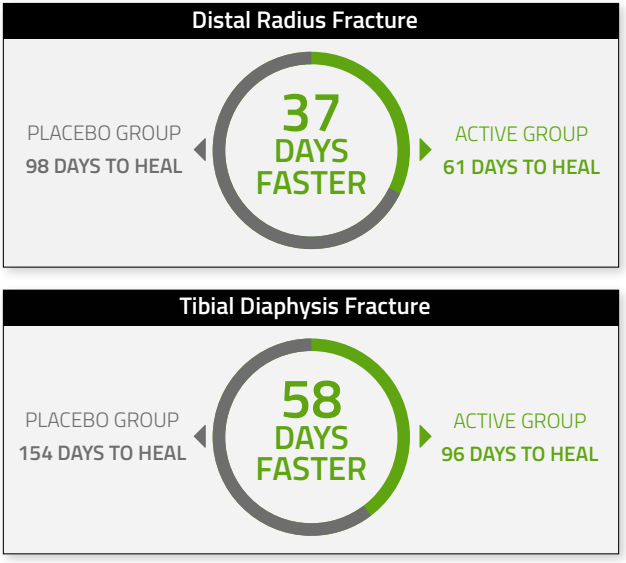
Fracture Healing

Clinical studies have validated the safety and effectiveness of LIPUS:

Clinical studies on LIPUS have successfully shown to resolve 86% of nonunion fractures and this treatment induced a 38% acceleration in achieving clinical and radiographic healing.[9,34-37]

Studies show the safety and effectiveness of the LIPUS for noninvasive treatment of established nonunions, fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures.[34-38] Treatment with LIPUS accelerated healing by 38% (96 days for LIPUS treated versus 154 days for control group).[34]

Faster healing in both cortical and cancellous bone



LIPUS has been proven to be a safe and effective noninvasive treatment to improve overall nonunion fracture healing success rates and to accelerate the healing of indicated fresh fractures.[34-36]

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Brief Prescribing Information:

The AccelStim device is indicated for the non-invasive treatment of established nonunions excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature adult individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

Full prescribing information can be found in product labeling on our patient education website BoneGrowthTherapy.com or by calling Patient Care at 800.535.4492. Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

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