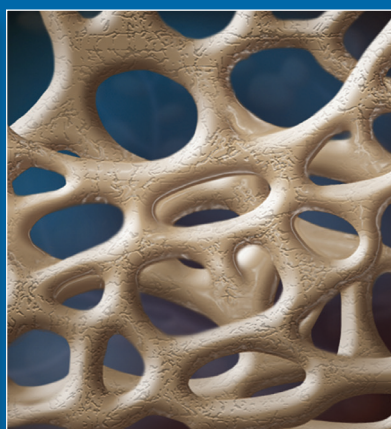
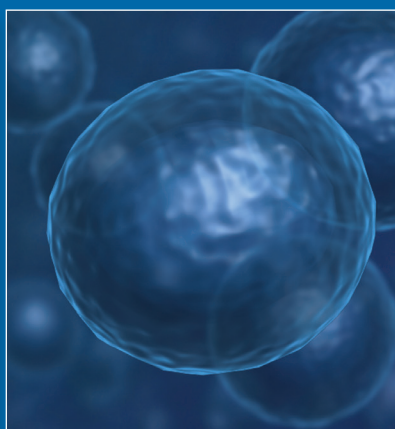
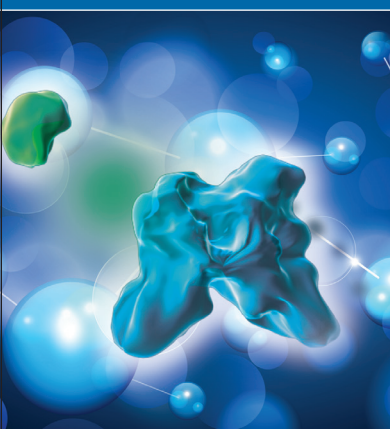


HOW PEMF WORKS

Orthofix Pulsed Electromagnetic Field Technology

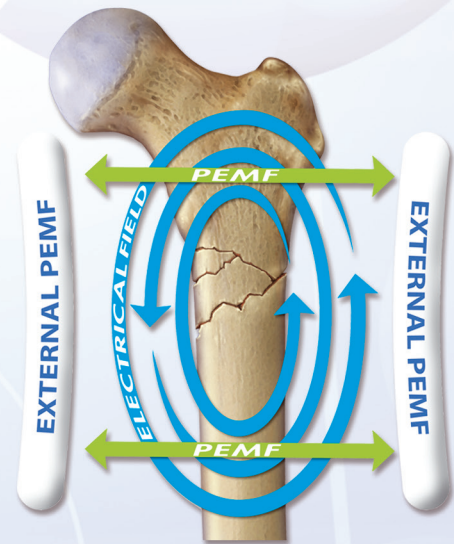


HOW PEMF STIMULATES FRACTURE REPAIR

How does PEMF affect bone healing?

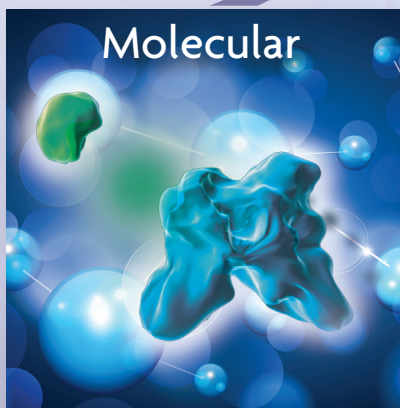
When human bone is bent or broken, it generates an electrical field. This low level electrical field stimulates bone healing.¹⁻³ For years it has been known that bone tissue is deposited in regions of negative charge and absorbed in areas of positive charge.⁴ PEMF induces a negative electrical field at the fracture site which supports the natural healing process and stimulates fracture repair.¹

In some patients this healing process is impaired or absent, and the fracture results in a nonunion. Electrical stimulation has been shown to dramatically increase the speed and completeness of bone healing in large or slowly healing fractures.⁵

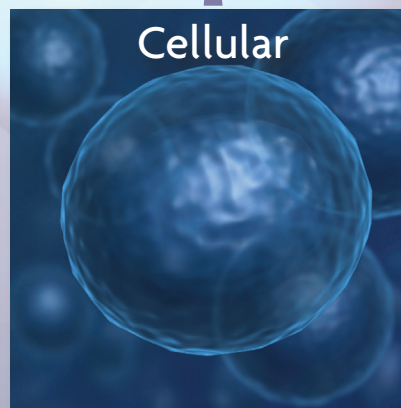


Orthofix Osteogenesis Stimulators use a unique PEMF signal to create a conducive environment for bone to heal.*

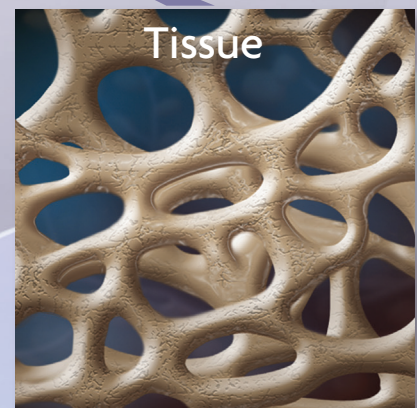
PEMF IMPACTS BONE HEALING AT A MOLECULAR, CELLULAR, AND TISSUE LEVEL



Within 10 minutes of PEMF exposure, signaling pathways are activated.⁶



PEMF stimulates bone cells to proliferate, differentiate, and mineralize.⁷



PEMF has been shown to improve the quality of bone tissue and enhance bone preservation.^{8,9}

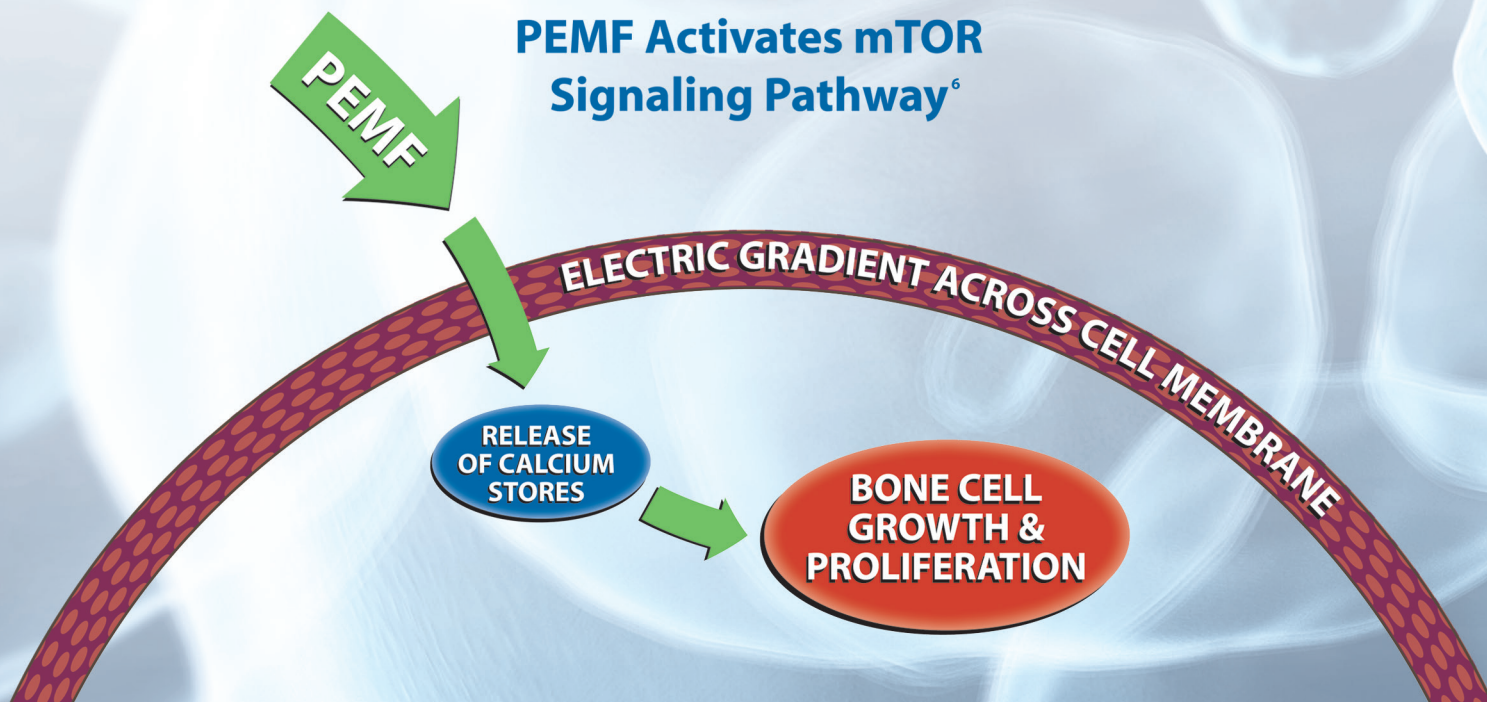
PEMF has been clinically proven to be a safe and effective noninvasive treatment to improve healing rates.^{10, 11}

HOW PEMF WORKS:

MOLECULAR LEVEL

Research on the molecular impact of PEMF demonstrates:^{6, 7, 12, 13}

- Exposure of a bone-forming cell (osteoblast) to PEMF generates an electric field gradient across the cell membrane¹²
- Following this activation, bone cells recognize PEMF with an immediate intracellular response⁶
- Similar to growth factors (PTH and Insulin), PEMF activates signaling pathways within minutes⁷
- Activating these signaling pathways with PEMF (PI3-mTor-p70-s6)⁶ results in cell growth, proliferation, and differentiation¹³



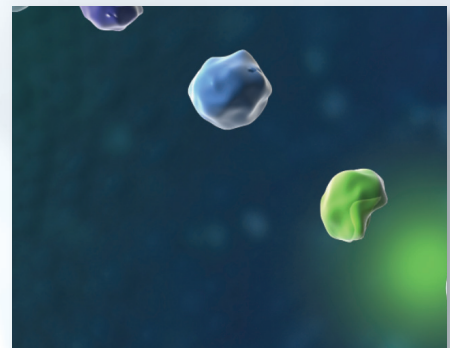
Within 10 minutes of PEMF exposure, signaling pathways are activated.^{*, 6}

HOW PEMF WORKS:

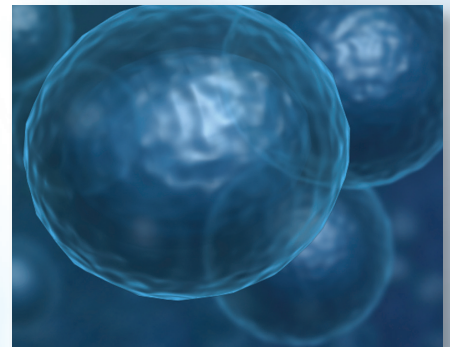
CELLULAR LEVEL

Research at The Cleveland Clinic and New York University have significantly advanced our understanding of how PEMF facilitates bone growth at the cellular level:^{6, 7, 13}

- PEMF treatment causes a significant increase in expression for genes involved in proliferation, differentiation, and mineralization¹³
- The use of PEMF and BMP-2 together has been documented to have an additive effect on cell growth and proliferation, which suggests that each intervention utilizes a separate intracellular signaling pathway^{6, 7, 13}



PEMF activates signaling pathways⁶



Bone cell growth and proliferation is enhanced¹³

PEMF stimulates bone cells to proliferate, differentiate, and mineralize.^{*, 7}

HOW PEMF WORKS:

TISSUE LEVEL

The application of PEMF has been documented to have a significant effect on bone tissue in animal studies completed at the Cleveland Clinic.^{8,9}

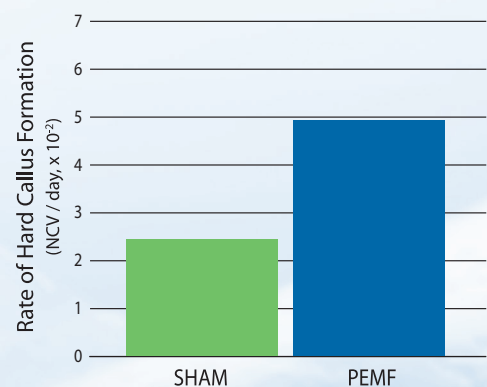
PEMF Increases Bone Volume and Quality⁸

- In a fibular fracture model (rat osteotomy), the group treated with PEMF was shown to have a 2-fold increase in bone volume 13-20 days postoperatively compared with the control group. A histological comparison between osteotomy sites revealed the bone quality was better in sites treated with PEMF.

PEMF Slows Bone Resorption in a Pre-Clinical Disuse Model⁹

- A separate study also utilizing a fibular fracture model (rat osteotomy) reported the group treated with PEMF experienced a 75% preservation of bone volume at the distal fibular end in comparison to controls.

Twice as Fast Callus Formation⁸



Notes:

- Significantly faster rate of callus formation for PEMF
- NCV = Normalized Callus Volume

PEMF has been shown to improve the quality of bone tissue and enhance bone preservation.^{*, 8, 9}

HOW PEMF WORKS:

BONE HEALING

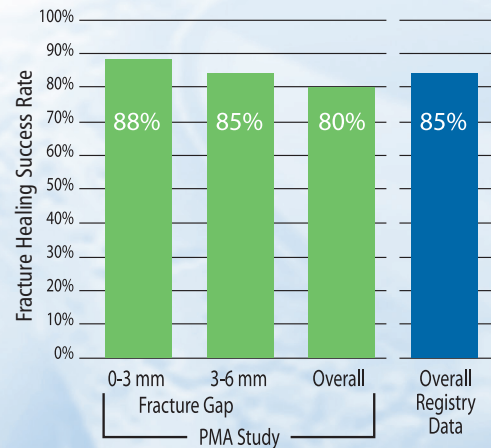
Clinical studies have validated the safety and effectiveness of Orthofix PEMF devices:^{10, 14}

In a prospective clinical trial, Garland et al confirmed the effectiveness of PEMF on fracture nonunions. A nonunion was defined as a fracture that failed to demonstrate both clinical and radiographic union at least nine months after the original insult.

When the PEMF unit was worn for 3 hours per day, there was an overall healing success rate of 82.7% in long bone nonunions without any additional surgery required. The results of the study also show that the success rate for fracture gaps 0-3mm was 88%, and the success rate for fracture gaps 3-6mm was 85%.¹⁰

In addition to the prospective clinical trial proving the safety and effectiveness for fracture nonunion, Orthofix conducted a 4-year follow-up on those patients who were prescribed the Physio-Stim device. After PMA approval was received, a Patient Registry was conducted. Both the long term follow-up and the registry confirm the high healing success rate reported in the original PMA study.^{10, 14}

Study Results^{10, 11, 14}



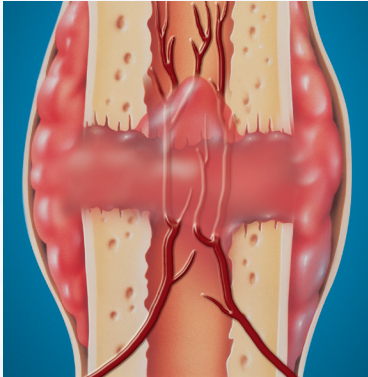
Proven Fracture Healing Success¹⁴

Femur	84.2%
Fibula	91.4%
Metatarsal	90.9%
Tibia	89.0%
Ulna	96.1%
Radius	93.8%

PEMF has been proven to be a safe and effective noninvasive treatment to improve overall bone healing success rates.^{10, 11, 14}

HOW PEMF WORKS:

FOUR PHASES OF BONE HEALING

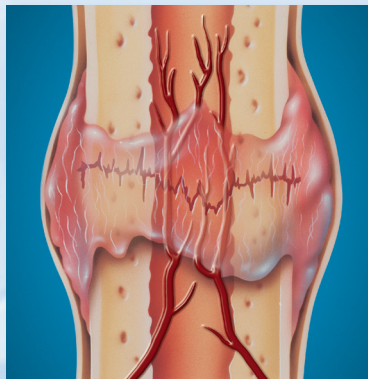


Phase 1: Hematoma

- 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.
- Tissue at the site becomes swollen and painful in response to inflammatory factors.
- New blood vessels begin to form to reestablish the blood supply.

PEMF Benefit

- PEMF stimulates an increase in vessel production.²



Phase 2: Formation of Soft Callus

- Inflammatory factors attract cells to the site.
- Cells remove the hematoma and bone debris.
- For healing to progress at this stage, the inflammatory response must cease.
- Cells begin reconstructing the bone by laying down matrix. Proteins and mineralization factors produced by the osteoblasts (bone forming cells) begin to consolidate into what is known as a soft callus.

PEMF Benefit

- PEMF amplifies calcium flux, which activates signal transduction pathways.^{5,15}
- Activated pathways increase the production of growth factors.⁵
- These growth factors promote healing by increasing the number and activity of osteoblasts.⁵



Phase 3: Formation of Hard Callus

- Osteoblasts mineralize the matrix, converting soft callus into hard callus.

PEMF Benefit

- PEMF treatment increases mineralization of this matrix and calcification of fibrocartilage.^{5,8}



Phase 4: Remodeling

- Woven bone is remodeled into stronger lamellar bone by the orchestrated action of osteoblast bone formation cells and osteoclast bone resorption cells.
- Eventually, the fracture callus is remodeled into a new shape which closely duplicates the bone's original shape and strength.

PEMF Benefit

- PEMF stimulates remodeling by increasing the rate of osteoblast activity.⁵

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*The results of preclinical studies may not be indicative of human clinical trials.

GLOSSARY

- **OSTEOBLASTS** – bone forming cells
- **OSTEOCLASTS** – cells that break down bone, involved in remodeling
- **GROWTH FACTOR** – a substance (typically a protein or a hormone) that stimulates growth of a cell population and stimulates maturity of the cell.
- **PROLIFERATION** – increase cell population/number of cells
- **DIFFERENTIATION** – maturity of the cells; only mature cells can be active/result in bone formation.
- **CYTOKINE** – protein signaling molecules involved in the inflammatory response.

PROVEN SUCCESS PULSED ELECTROMAGNETIC FIELD (PEMF)



Model 3202



Model 3303



Model 3313



Model 3314



Model 3315



Brief Prescribing Information:

The Physio-Stim® is indicated for the treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than one-half the width of the bone to be treated. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

Use of this device is contraindicated where the individual has synovial pseudarthrosis. Demand type pacemaker operation may be adversely affected by exposure to pulsed electromagnetic fields. The safety and effectiveness of this device has not been established for individuals lacking skeletal maturity or individuals with a nonunion secondary to, or in connection with, a pathological condition. The safety of this device for use on patients who are pregnant or nursing has not been established. Rare instances of reversible minor discomfort have been reported.

Full prescribing information can be found in product labeling on our patient education website www.bonestimulation.com or by calling Patient Services at 1-800-535-4492.

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

1.800.555.4492

www.orthofix.com

www.bonestimulation.com

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