

A Review - Does Low Magnitude High-Frequency Vibration (LMHFV) Worth for Fracture Recovery Compared with Pulsed Electromagnetic Field (PEMF) Based Magnetotherapy Method?

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The subject of electromagnetic fields is widespread today, including in the medical world. One of them is therapy in fracture healing using the Pulsed Electromagnetic Field (PEMF) method by utilizing a magnetic field. Fracture healing using the magnetic field method utilizes the Helmholtz coil, which is influenced by the current and the amount of turns flowing in the magnetic field. This study conducted a literature study on fracture healing using the PEMF and the LMHFV methods. A comparison of these two methods will show different healing effects. From the studies, we can conclude which way has the most advantage in healing. A faster rehabilitation process will have an impact on reducing implant failure. In contrast, Applying the LMHFV method to bone fractures gives more significant and faster results in bone formation in the damaged part, and the healing process is owned faster. From these two methods, it can be concluded that the LMHFV method provides a similar healing effect than the PEMF method. Applying the LMHFV and PEMF method to bone fractures gives more significant and faster results in bone formation in the damaged part. In addition, the healing process is owned faster.

Keywords: Fractures; Magnetotherapy; LMHFV; PEMF.

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I. INTRODUCTION

Fracture is a term for loss of continuity of bone and cartilage, either total or partial. In general, trauma or physical exertion that damages the bone might lead to fracture. [1-4]. The most common fractures cause is work-related, traffic accidents, and simple accidents that cause bone damage. Apart from accidents, fractures can also occur due to other factors such as degenerative processes and bone pathology [5-6]. Specifically, bone fractures can present in three locations: the diaphysis (middle section), the head/neck of the bone, or close to the knee (lower end) [7]. In addition to fractures, bone damage in humans includes osteoporosis, which is caused by age factors that will cause other bone damage. *Osteoporosis* is an age-related condition that causes gradual bone loss and brittle bone [1]. It is a significant global medical, social, and economic issue that affects older persons' health. A substantial risk of osteoporotic fractures exists in patients with osteoporosis [8-10].

Fractures/bone damage that occurs can be cured by one of the methods of physiotherapy treatment [11-13]. Magnetotherapy is one of the most popular physiotherapy methods successfully used in orthopaedics and rheumatology. Magnetotherapy can relieve pain and shorten the healing time for fractured bone tissue [14-17]. The formation of tissue (osteogenesis) bone can be accelerated by conducting a mag-

netotherapy process. That produces microcurrents which significantly stimulate the trophic formation of bone and collagen [18-21]. The basic principle of electromagnetic induction is the working principle of magnetotherapy. By using a time-varying magnetic field produced by a time-varying electric current flowing through a coil positioned in an anatomical region, magnetotherapy was performed [22-25]. The electric field in the network is generated from the magnetic field. It depends on the magnetic field's characteristics applied to the network's properties during the magnetic field effect [26]. Electromagnetic-based medical therapy tools include various devices that generate electricity and magnetic fields. Transcutaneous Electrical Nerve Stimulation (TENS), Neuromuscular Electrical Stimulation (NMES), High Voltage Pulsed Galvanic (HVPG) and Pulse Electromagnetic Field (PEMF) are some medical tool which utilizes the concepts of electricity and magnetism [27]. TENS, NMES and HVPG generate an electric field in the tissue directly due to an electric current flowing through the two electrodes placed on the target tissue so that it is semi-invasive. PEMF is a non-invasive and inductive technique in which an electric field is generated in the tissue due to a changing magnetic field [28-30].

PEMF (Pulsed Electromagnetic Field) is a method of fracture healing process based on electromagnetic fields. The Helmholtz coil used in the electromagnetic field test has a magnetic field value influenced by the current and the amount

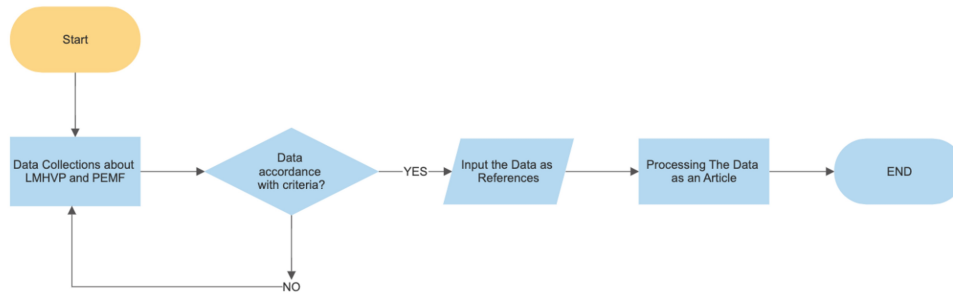


FIG. 1: Data Process Collection.

of turns, which is related to the fracture healing process [31,32]. According to Hasnia *et al.*, coil diameters affect current fluctuation, distance variations, and magnetic field changes that rely on the number of coils [33]. According to the Biot-Savart equation, the magnetic field at a distance x from the coil is inversely proportional to the number of turns and will be as follows:

$$B = \frac{\mu_0 N I R^2}{2(R^2 + x^2)^{3/2}} \quad (1)$$

A well-known and effective theoretical method for calculating magnetic fields due to currents in magnetostatics is the Biot-Savart law. By deriving a law similar to the Biot-Savart law and appropriate for calculating electric fields, we expand the scope of application and The Biot-Savart law's formal formulation in electrostatics [35]. We demonstrate how the classic Dirichlet problem can occasionally be reduced to a more straightforward Biot-Savart-like problem. In an otherwise grounded plane, we discover an integral expression for the electric field caused by a randomly formed planar area maintained at a fixed electric potential [36]. We also provide a reasonably straightforward method for computing the field generated in the plane formed by such an area as a byproduct. By analyzing the electric field produced by a few non-trivial forms' planar portions, we demonstrate the value of our method. [37-38]

According to Ongaro *et al.* [13], based on approval from the Food and Drug Administration (FDA), one of the processes for using PEMF is to help heal non-union fractures. About 10% of the healing process of incomplete bone fracture symptoms causes non-union and delayed union because of the increased mobility of the population [34]. PEMF research has been conducted for an extended period in vitro (cell research), pre-clinically (tested animal studies), and clinically [36]. In line with Ongaro *et al.*, they provided an exposure-based physical stimulation to PEMF (1.5 mT, 75 Hz) for 28 days (the period of differentiation of bone cells, namely [37]. The results obtained were increased levels of Alkaline phosphatase (ALP) and Osteocalcin (OCL), which were the response to the occurrence of bone formation (osteogenesis)[38].

In addition to the positive things, there are concerns about the negative impacts caused by the results of the magnetic field characteristics [39]. From these conditions, the

World Health Organization or the World Health Organization (WHO), the recommended value of exposure to magnetic fields is $100 \mu T - 500 \mu T$ [34]. Therefore, PEMF with magnetic field values following WHO recommendations must be developed more significantly.

In contrast to the PEMF method, the LMHFV method is also used in the fracture therapy process using the magnetic field method[40-45]. When LMHFV was performed at 35 Hz, 0.3 g, the healing process for both normal and osteoporotic bone demonstrated an improved acceleration of the healing process by reformed production of callus and mineralization[46-52, 8-12]. Chow D.H. *et al.* confirmed that LMHFV enhances fracture healing, stimulates bone remodelling, and has excellent potential for clinical improvement in fracture recovery [8-12]. Whole-body mechanical stimulation is provided using low-magnitude high-frequency vibration (LMHFV), a minimally invasive biophysical procedure [17-20]. Previous research showed the positive effects of LMHFV on blood circulation, spinal bone mineral density (BMD), new bone formation, postural control, and muscle strength [10].

II. METHOD

This review was conducted following these investigations' information, statement, and outcomes. Search engines were used to electronically search databases without regard to language, publishing, or geographic restrictions. Each database search combines concepts and subject headings. For search criteria, we used keywords LMHFV and PEMF and the therapy by using both methods. The fracture of bone for clinical use with LMHFV and PEMF method for therapy was used for search criteria.

III. RESULTS AND DISCUSSION

The research from PEMF and HMVP results shows that mechanism work involves many ways. Clinical issues have prompted the development of mechanical stimulation techniques, such as LMHFV and PEMF [17], to improve bone healing; However, the detailed mechanism by which these

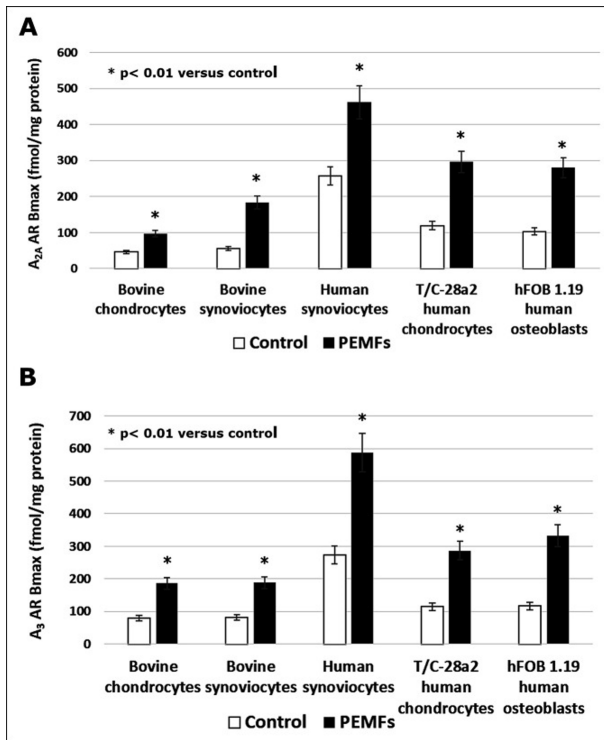


FIG. 2: The presence and absence of Pulsed electromagnetic field (PEMF) stands for adenosine receptor shown as a bar graph. [20]

methods enhance tissue repair and provide anabolic stimulus is still unknown [2]. A recent study compared and evaluated the effectiveness of LMHFV and PEMF as two treatment approaches for bone remodelling [20-24]. The study discovered that LMHFV induced callus angiogenesis [12,43,51]. Because LMHFV provides a non-invasive treatment that can increase bone mass, vibration applications can be easily used for individuals with limited mobility and have nearly no contraindications [19]. On the other hand, it was also shown that the healing of sheep metatarsal fractures was not significantly affected by ground-based vibrations on a platform with 20 Hz [16]. According to Lei T et.al.[15], A combination of increased bone formation and decreased bone resorption linked to the regulation of skeletal gene expression via the Wnt3a/LRP5/-catenin and OPG/RANKL/RANK signaling pathway, long-term PEMF stimulation was able to relieve osteoporosis in the lumbar spine of postmenopausal rats [21].

Mice with shattered bones repaired had woven bones that fully developed, dense trabeculae, and active bone marrow. They had a significantly higher BV/TV ratio than the control group ($p = 0.01$). This progress indicates that HF-PEMF treatment aids bone healing more quickly [13-16, 21-32]. For two weeks after surgery, HF-PEMFs were applied daily for 10 minutes to rats. This improved bone consolidation, especially in the early stages of fracture repair [22]. Applying HF-PEMFs to rats starting on the first postoperative day for 10 minutes a day for two weeks can increase bone consolidation, particularly during the initial stages of fracture repair.

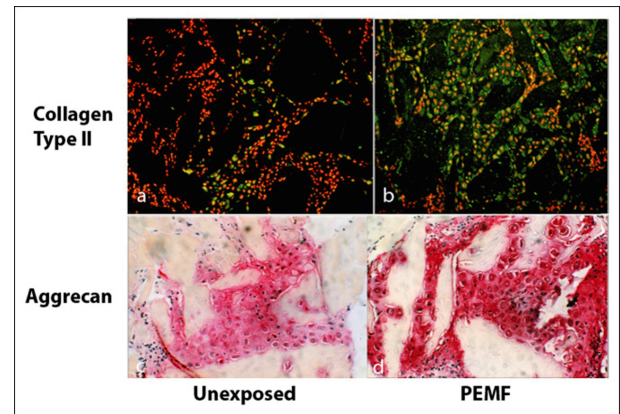


FIG. 3: Shows result of the type II collagen and aggrecan immunohistochemistry in the DBM-EO model with and without PEMF exposure. (Reproduce with permission from Cadossi et.al) [22]

This treatment shows that the mending of fractures is taking place [40]. Most earlier investigations into the physiologic effects of PEMF on bone healing were qualitative evaluations of the amount of newly produced bone, with very few quantitative measurements [36-39]. The findings of the three-point breaking experiment (mechanical strength and elastic deformation), imaging measurements (TV, BV, and BV/TV), and serum markers were all employed by Zhou J in a study to determine the quantitative bone formation criterion (ALP and OC) [3]. Fig. 2 shows that PEMFs treatment gives a result that there is an increase in the density of Bovine compared to control bovine. The presence and absence of PEMF shows in (A) The density of A_{2A} AR (A) and (B) the density of A₃ AR in bovine chondrocytes and synoviocytes, human synoviocytes, T/C-28a2 human chondrocytes, and hFOB 1.19 human osteoblasts [20]. Figure 3 shows the improvement of collagen and aggrecan after PEMF treatment compared with non-exposed PEMF. DBM particles are displayed as black patches in (A and B) and bright areas in (C and D). By stimulating PEMF, both ECM molecules are raised. Extracellular matrix, demineralized bone matrix, endochondral ossification, and pulsed electromagnetic field all refer to the same thing [22]. Fig. 2 and 3 show bone improvement the fracture and collagen after PEMF treatment. This is can be concluded that PEMF treatment improves the healing process in damaged bones or other parts. The bone healing process improves significantly. There are four crucial stages to the callus-based bone healing process. A hematoma forms at the location of the bone injury during the first phase, which starts right after the fracture. The second phase, referred to as the inflammatory phase, is when inflammatory cell clusters and cells from various lineages form at the site of the shattered bone. These cells produce cytokines and growth factors that initiate the healing process. The third stage entails the development and mineralization of the callus that will span the gap in the bone. The mineralized callus is replaced with mineralized bone during the final stage of bone healing. The bone is then modelled and remodelled to restore its previous form and biomechanical competency [41]. The second phase, referred

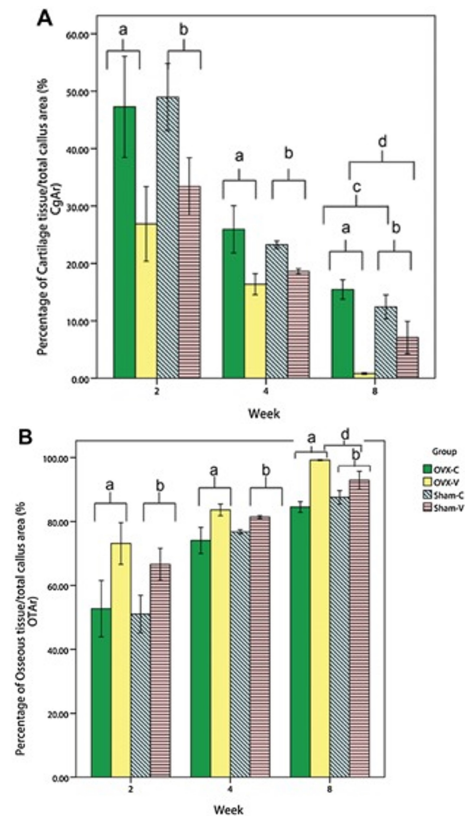


FIG. 4: The percentage shifts in osseous and cartilaginous regions from the second to the eighth week. [12]

to as the inflammatory phase, is when inflammatory cell clusters and cells from various probability of transitioning to THA within five years following PEMF was 16% overall, according to Kaplan-Meier survivorship analysis. A considerably more significant conversion rate to THA was observed in patients with the necrotic lesion laterally, in subgroup C (more than 30% involvement of necrosis), and patients older than the mean age.s lineages form at the site of the shattered bone. These cells produce cytokines and growth factors that initiate the healing process [12].

A stereology investigation found that LMHFV is a mechanical stimulation that promotes osteogenic effects [17-20]. In addition to delivering anabolic signals and raising both anabolic and osteogenic signals, it will increase the entire bone area and new tissue area to improve biomechanical strength [22]. This result is in line with what Chow *et al* [8-9]. reported, and it shows how cyclic stimulation speeds up the growth of embryonic cartilage during enchondral ossification. Because more tibial bone was formed in the LMHFV group, it may be concluded that the treatment successfully enhanced fracture healing by promoting callus production [42].

Low-magnitude high-frequency vibration (LMHFV), a non-pharmacological medical treatment, has shown to positively impact bone induction and remodelling for various muscle diseases in animal studies [41-51]. Show that LMHFV is a valuable method for enhancing osseointegration clinically, particularly for osteoporosis [43]. By controlling the expres-

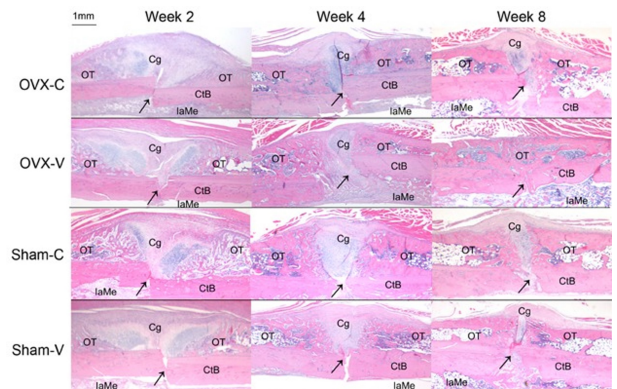


FIG. 5: Typical photomicrographs of the histomorphology of the callus in the OVX and Sham groups at weeks 2, 4, and 8. [12]

sion of genes involved in several genes, it was expected that LMHFV might accelerate the repair of osteoporotic fractures [44]. This experiment examined the impact of LMHFV treatment on the healing process. The osteoporotic and healthy bone fractures were treated by histomorphometry, weekly radiography, and endpoint gene expressions [50-52]. This treatment shows increases the expression of genes associated with chondrogenesis, osteogenesis, and remodelling; LMHFV improved the healing of osteoporotic fractures [45]

Rats with osteoporosis and normal rats both responded favourably to low-magnitude high-frequency vibration (LMHFV), according to Chow *et al.* (35 Hz, 0.3 g), which promotes callus development and mineralization, and speeds up the healing of fractures [41-51]. We predicted that LMHFV accelerates bone remodelling during fracture repair. Ibandronate attenuated LMHFV-stimulated bone remodelling and alterations in remodelling have been studied. The femora were extracted, and the blood was obtained for histological and radiological examinations. The callused area (CA), callus width (CW), and bone volume to tissue volume ratio (BV/TV) decreased in VG at the fastest rate, while BG and VBG showed a plateaued trend. Week 6 had the most significant mineral apposition percentage, quickest callus reduction, and higher osteocalcin and TRAP5b serum concentrations in VG supported accelerated remodelling. The fact that LMHFV partially overrode ibandronate's suppression of bone remodelling showed that LMHFV harmed bone remodelling [9].

Mineralization and remodelling on fracture were compared to OVX-C, it was enhanced by 25–30%, and the energy to failure was raised by 70–80%. The results of this study offer a solid foundation for the proposition that starting clinical trials is the next step in assessing the effectiveness of LMHFV on osteoporotic fracture repair [41].

Fig. 4 shows the percentage changes of cartilage with LMHFV treatment. There were correlations between (a) OVX-C and (b) OVX-V, (c) OVX-C and (d) OVX-V and (e) Sham-C and Sham-V. ($p < 0.05$ overall) (error bar = 1 SD) [12] Fig. 5 shows the callus condition after LMHFV treatment, compared with different osseous tissue. From week 2 to week 4, the area of cartilaginous tissue (Cg) in all samples' cal-

lus decreased while the area of osseous tissue (OT) increased (OVX-V and Sham-V). At week 8, vibration groups outperformed control groups in remodelling, and more OVX-V samples had completed callus bridging. (H&E, X16 magnification) (The arrowhead indicates the fracture position.) Cg is an abbreviation for cartilaginous tissue, OT for osseous tissue, CtB for cortical bone, and IaMe for an intramedullary canal [12].

In summary, LMHFV enhances fracture healing by improving bone remodelling; ibandronate administration can reduce this improvement. LMHFV offers a considerable deal of potential for clinically improving fracture outcomes [40-45]. The stimulatory action can lessen the frequency of non-union or delayed union, which is frequent in open fractures. The patient can resume function following the fracture, which will allow for quicker rehabilitation [46-50]. The rapid fracture healing rate will decrease the implant failure rate. Based on the primary findings and additional metrics, the results suggest that immediate treatment of LMHFV to the fracture site stimulates bone production and healing better than PEMF application [24-31]. Vibration therapy may hasten fractures' healing by encouraging calluses' growth. These data suggest that vibration therapy's anabolic effect on fracture repair may

have numerous therapeutic implications [36-39].

IV. CONCLUSION

Based on literature studies that have been carried out on the use of magnetotherapy for recovery in patients with fractures, it is inevitable that the use of PEMF and LMHFV methods has proven to be effective. Tests on white rats using PEMF showed a molecular acceleration of fracture healing, continuously and intermittently. In the LMHFV therapy method, callus angiogenesis can increase bone formation and has a faster healing period. The Control group experienced less callus formation than the PEMF and LMHFV groups, despite the fact that the contrast was not statistically significant. In comparison to control, Serum levels of osteocalcin were more significant in the experimental groups, particularly in the LMHFV group. The results of the current investigation suggest that direct local LMHFV injection has promoted bone development and has the potential to improve fracture outcomes dramatically.

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- [1] A. Oryan, S. Monazzah, and A. Bigham-Sadegh, "Bone injury and fracture healing biology," *Biomed. environment. Sci.*, vol. 28, no. 1, pp. 57-71, 2015, doi: 10.3967/bes2015.006.
- [2] A. Krawczy, P. Murawski, E. Korzeniewska, "Medical and technical analysis of magnetotherapeutical Devices," *IEEE Int. conf. on Modern Electrical and Energy Systems (MEES)*, 15-17 Nov. 2017.
- [3] D. D. Thomson, "Introduction-Mechanisms of fracture healing and pharmacologic control," *J. Musculoskelet Neuronal Interact.* 2003 Dec;3(4):295-6. PMID: 15758303.
- [4] R. K. Aaron, B. Boyan, D. M. Ciombor, *et al.* "Stimulation of growth factor by electric and electromagnetic fields," *Clin. Orthop. Rel. Res.* 2004;419:30-37.
- [5] R. G. Bacabac, T. H. Smit, J. J. Van Loon, *et al.* "Bone cell responses to high-frequency vibration stress: does the nucleus oscillate within the cytoplasm?," *FASEB J.* (2006),20, 858-864. doi: 10.1096/fj.05-4966.com.
- [6] A. Shibamoto, T. Ogawa, J. Duyck, *et al.* "Effect of high-frequency loading and parathyroid hormone administration on peri-implant bone healing and osseointegration," *Int. J. Oral Sci* (2018). 10:6. doi: 10.1038/s41368-018-0009-y
- [7] B. Wade, "A review of pulse electromagnetic field mechanism at a cellular level : a rationale for clinical use", *American J. of Health Research*, 2013; 1(3):51-55
- [8] D.H. Chow, K.S. Leung, L. Qin, *et al.* "Low-magnitude high-frequency vibration (LMHFV) enhances bone remodelling in osteoporotic rat femoral fracture healing," *J Orthop Res.* 2011 May;29(5):746-52. doi: 10.1002/jor.21303. Epub 2010 Dec 23. PMID: 21437955.
- [9] S.K.H. Chow, C.Y. Ho, H.W. Wong, *et al.* "Efficacy of low-magnitude high-frequency vibration (LMHFV) on musculoskeletal health of participants on wheelchair: a study protocol for a single-blinded randomised controlled study," *BMJ Open*. 2020 Dec 15;10(12):e038578. doi: 10.1136/ BMJ open-2020-038578. PMID: 33323430; PMCID: PMC7745337.
- [10] H.F. Shi, W.H. Cheung, L. Qin, *et al.* "Low-magnitude high-frequency vibration treatment augments fracture healing in ovariectomy-induced osteoporotic bone," *Bone*, 2010, Volume 46, Issue 5, Pages 1299-1305, ISSN 8756-3282, <https://doi.org/10.1016/j.bone.2009.11.028>.
- [11] X. Ye, Y. Gu, Y. Bai, *et al.* "Does Low-Magnitude High-Frequency Vibration (LMHFV) Worth for Clinical Trial on Dental Implant? A Systematic Review and Meta-Analysis on Animal Studies," *Front. Bioeng. Biotechnol.* 2021, 9:626892. doi: 10.3389/fbioe.2021.626892
- [12] S.L. Chung, K.S. Leung, and W.H. Cheung, "Low-magnitude high-frequency vibration enhances gene expression related to callus formation, mineralization and remodelling during osteoporotic fracture healing in rats," *J. Orthop. Res.*, (2014), 32: 1572-1579. <https://doi.org/10.1002/jor.22715>
- [13] A. Ongaro, A. Pellati, L. Bagheri, *et al.* "Pulsed Electromagnetic Fields Stimulate Osteogenic Differentiation in Human Bone Marrow and Adipose Tissue-Derived Mesenchymal Stem Cells," New York: Bioelectromagnetic Wiley Periodical, 2014, pp 426-436
- [14] L. S. Freedman, "Pulsating electromagnetic fields in the treatment of delayed and non-union of fractures: results from a district general hospital," *Injury*. 1985, 16 (5): 315-317. 10.1016/0020-1383(85)90134-2.
- [15] T. Lei, Z. Liang, F. Li, *et al.* "Pulsed electromagnetic fields (PEMF) attenuate changes in vertebral bone mass, architecture and strength in ovariectomized mice," 2018 Mar;108:10-19. doi: 10.1016/j.bone.2017.12.008. Epub 2017 Dec 8. PMID: 29229438.
- [16] D. Oltean-Dan, G. B. Dogaru, D.Apostu, *et al.* "Enhancement of bone consolidation using high-frequency pulsed electromagnetic fields (HF-PEMFs): An experimental study on rats," *Bosn. J. of B Med Sciences*, (2019). 19(2), 201-209.

- <https://doi.org/10.17305/bjbmms.2019.3854>
- [17] F.Y. Wei, S.K. Chow, K.S. Leung, *et al.* "Low-magnitude high-frequency vibration enhanced mesenchymal stem cell recruitment in osteoporotic fracture healing through the SDF-1/CXCR4 pathway," *Eur Cell Mater.* 2016 May 24;31:341-54. doi: 10.22203/ecm.v031a22. PMID: 27215741.
- [18] Q. Zhao, Y. Lu, X. Gan, H. Yu, "Correction: Low magnitude high frequency vibration promotes adipogenic differentiation of bone marrow stem cells via P38 MAPK signal," *PLOS ONE* (2017) 12(12): e0189547. <https://doi.org/10.1371/journal.pone.0189547>
- [19] W.R. Thompson, B.V. Keller, M.L. Davis, *et al.* "Low-Magnitude, High-Frequency Vibration Fails to Accelerate Ligament Healing but Stimulates Collagen Synthesis in the Achilles Tendon," *Orth. J. of Sp. Med.* 2015. doi: 10.1177/2325967115585783
- [20] K. Varani, F. Vincenzi, A. Ravani, *et al.* "Adenosine receptors as a biological pathway for the anti-inflammatory and beneficial effects of low frequency low energy pulsed electromagnetic fields," *Mediators Inflamm.* 2017;2017:2740963.
- [21] J. Zhou, H. He, L. Yang, "Effects of pulsed electromagnetic fields on bone mass and Wnt/ β -catenin signaling pathway in ovariectomized rats," *Arch Med Res.* 2012 May;43(4):274-82. doi: 10.1016/j.arcmed.2012.06.002. Epub 2012 Jun 13. PMID: 22704852.
- [22] Cadossi, *et al.* "Pulsed Electromagnetic Field Stimulation of Bone Healing and Joint Preservation: Cellular Mechanisms of Skeletal Response," *JAAOS: Global Research and Reviews: May 2020 – Vol. 4 - Issue 5 - p e19.00155* doi: 10.5435/JAAOSGlobal-D-19-00155
- [23] M.C. Yoo, Y.J. Cho, K.I. Kim, *et al.* "Pulsed Electromagnetic Fields Treatment for The Early Stage of Osteonecrosis of The Femoral Head," *Orthopaedic Proceedings* Vol. 86-B, No. SUP-II
- [24] B. Chalidis, N. Sachinis, A. Assiotis, G. Maccauro, "Stimulation of bone formation and fracture healing with pulsed electromagnetic fields: biologic responses and clinical implications," *Int J Immunopathol Pharmacol.* 2011 Jan-Mar;24(1 Suppl 2):17-20. doi: 10.1177/03946320110241S204. PMID: 21669132.
- [25] X.S. Qiu, X.G. Li, Y.X. Chen, "Pulsed electromagnetic field (PEMF): A potential adjuvant treatment for infected nonunion," *Med Hypotheses.* 2020 Mar;136:109506. doi: 10.1016/j.mehy.2019.109506. Epub 2019 Nov 18. PMID: 31841766.
- [26] H.R. Gossling, R.A. Bernstein, J. Abbott, "Treatment of ununited tibial fractures: a comparison of surgery and pulsed electromagnetic fields (PEMF)," *Orthopedics.* 1992 Jun;15(6):711-9. doi: 10.3928/0147-7447-19920601-08. PMID: 1608864.
- [27] D. Bartolomeo, F. Cavani, A. Pellacani, "Pulsed Electromagnetic Field (PEMF) Effect on Bone Healing in Animal Models: A Review of Its Efficacy Related to Different Type of Damage," *Biology (Basel).* 2022 Mar 5;11(3):402. doi: 10.3390/biology11030402. PMID: 35336776; PMCID: PMC8945722.
- [28] C. Daish, R. Blanchard, K. Fox, *et al.* "The Application of Pulsed Electromagnetic Fields (PEMFs) for Bone Fracture Repair: Past and Perspective Findings," *Ann Biomed Eng* 46, 525–542 (2018). <https://doi.org/10.1007/s10439-018-1982-1>
- [29] H.B. Murray, B.A. Pethica, "A follow-up study of the in-practice results of pulsed electromagnetic field therapy in the management of nonunion fractures" *Orthop Res Rev.* 2016;8:67-72. <https://doi.org/10.2147/ORR.S113756>
- [30] L. Caliogna, M. Medetti, V. Bina, *et al.* "Pulsed Electromagnetic Fields in Bone Healing: Molecular Pathways and Clinical Applications," *Int. J. Mol. Sci.* 2021, 22, 7403. <https://doi.org/10.3390/ijms22147403>
- [31] C.G. Lee, C. Park, S. Hwang, *et al.*, "Pulsed Electromagnetic Field (PEMF) Treatment Reduces Lipopolysaccharide-Induced Septic Shock in Mice," *Int J Mol Sci.* 2022 May 18;23(10):5661. doi: 10.3390/ijms23105661. PMID: 35628471; PMCID: PMC9147061.
- [32] H.M. Bilgin, F. Çelik, M. Gem, *et al.* "Effects of local vibration and pulsed electromagnetic field on bone fracture: A comparative study," *Bioelectromagnetics*, (2017) 38: 339-348. <https://doi.org/10.1002/bem.22043>
- [33] M. Hasmia, L. Mahmudin, A. Nismayanti, "Design of Electromagnetic Field Based Device Device for Fracture Therapy," *Gravity*, 2021, Vol. 20, No. 1, pp. 1-4.
- [34] WHO, "Electromagnetic fields and public health," *Electromagnetic fields (EMF) Publications and information resources*, 2006.
- [35] M. H. Oliveira and J. A. Miranda, "Biot-Savart-like law in electrostatics," *Eur. J. Phys.*, vol. 22, no. 1, pp. 31–38, 2001, DOI: 10.1088/0143-0807/22/1/304.
- [36] H.f. Shi, J. Xiong, Y. Chen, *et al.* "Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study," *BMC Musculoskelet Disord* (2013), 14, 35 <https://doi.org/10.1186/1471-2474-14-35>
- [37] C.C. Lin, R.W. Lin, C.W. Chang, G.J. Wang, K.A. Lai, "Single-pulsed electromagnetic field therapy increases osteogenic differentiation through Wnt signaling pathway and sclerostin downregulation," *Bioelectromagnetics* 2015;36:494-505.
- [38] S. Adie, I.A. Harris, *et al.* "Pulsed electromagnetic field stimulation for acute tibial shaft fractures: a multicenter, double-blind, randomized trial," *J Bone Joint Surg Am.* 2011, 93 (17): 1569-1576. 10.2106/JBJS.J.00869.
- [39] B.J. Punt, P.T. den Hoed, W.P.J. Fontijne. "Pulsed electromagnetic fields in the treatment of nonunion" *Eur J Orthop Surg Traumatol.* 2008, 18 (2): 127-133. 10.1007/s00590-007-0271-8.
- [40] L. Steppe, A. Liedert, A. Ignatius, H. M. Luntzer, "Influence of Low-Magnitude High-Frequency Vibration on Bone Cells and Bone Regeneration" *Frontiers in Bioengineering and Biotechnology*, (2020). 8. 10.3389/fbioe.2020.595139.
- [41] Z. Fu, H. Xu, W. Bo Pengcheng, C. Long, W. Xinyu, Z. Dong. "Protective effects of low-magnitude high-frequency vibration on high glucose-induced osteoblast dysfunction and bone loss in diabetic rats" *J. of Orthopaedic Surgery and Research.* (2021). 16. 10.1186/s13018-021-02803-w.
- [42] B. Chen, T. Lin, X. Yang, *et al.* "Low-magnitude, high-frequency vibration promotes the adhesion and the osteogenic differentiation of bone marrow-derived mesenchymal stem cells cultured on a hydroxyapatite-coated surface: the direct role of Wnt/ β -catenin signaling pathway activation" *Int. J. Mol. Med.* (2016). 38, 1531–1540. doi: 10.3892/ijmm.2016.2757
- [43] J. Gao, H. Gong, X. Huang, *et al.* "Multi-level assessment of fracture calluses in rats subjected to low-magnitude high-frequency vibration with different rest periods," *Ann. Biomed. Eng.* (2016). 44, 2489–2504. doi: 10.1007/s10439-015-1532-z
- [44] E. Lau, S. Al-Dujaili, A. Guenther, *et al.* "Effect of low-magnitude, high-frequency vibration on osteocytes in the regulation of osteoclasts," *Bone* (2010). 46, 1508–1515. doi: 10.1016/j.bone.2010.02.031
- [45] K. S. Leung, C. Y. Li, *et al.* "Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture

- risks in 710 community elderly—a cluster-randomized controlled trial,” *Osteoporos Int.* (2014). 25, 1785–1795. doi: 10.1007/s00198-014-2693-6
- [46] Y. Q. Liang, M. C. Qi, J. Xu, *et al.* “Low-magnitude high-frequency loading, by whole-body vibration, accelerates early implant osseointegration in ovariectomized rats,” *Mol. Med. Rep.* (2014). 10, 2835–2842. doi: 10.3892/mmr.2014.2597
- [47] S. Judex, X. Lei, D. Han, C. Rubin, “Low-magnitude mechanical signals that stimulate bone formation in the ovariectomized rat are dependent on the applied frequency but not on the strain magnitude,” *J Biomech.* 2007;40(6):1333-9. doi: 10.1016/j.jbiomech.2006.05.014. Epub 2006 Jun 30. PMID: 16814792.
- [48] H. M. Luntzer, Lackner I, Liedert A, Fischer V, Ignatius A. “Effects of low-magnitude high-frequency vibration on osteoblasts are dependent on estrogen receptor α signaling and cytoskeletal remodelling,” *Biochem Biophys Res Commun.* 2018 Sep 18;503(4):2678-2684. doi: 10.1016/j.bbrc.2018.08.023. Epub 2018 Aug 7. PMID: 30093109.
- [49] E. Wehrle, A. Liedert, A. Heilmann, *et al.* “The impact of low-magnitude high-frequency vibration on fracture healing is profoundly influenced by the oestrogen status in mice,” *Dis Model Mech* 2015; 8 (1): 93–104. doi: <https://doi.org/10.1242/dmm.018622>
- [50] S. Chung, W. Cheung, K. Leung “Gene expression of osteoporotic fracture healing augmented by low-magnitude high-frequency vibration treatment. *In ORS Annual Meeting*, (2012). San Francisco, CA, Poster No 1404.
- [51] K. S. Leung, H. F. Shi, W. H. Cheung, *et al.* “Low-magnitude high-frequency vibration accelerates callus formation, mineralization, and fracture healing in rats,” *J. Orthop. Res.* (2009). 27, 458–465.
- [52] W. R. Thompson, B. V. Keller, M. L. Dahners, “Low-magnitude, high-frequency vibration fails to accelerate ligament healing but stimulates collagen synthesis in the achilles tendon,” *Orthop. J. Sports Med.* (2015). 3:2325967115585783. doi: 10.1177/2325967115585783