



# HUMAN HEALTH BENEFITS OF LOW MAGNITUDE MECHANICAL STIMULATION (LMMS)

## LOW-MAGNITUDE MECHANICAL STIMULATION (LMMS)

- Low-magnitude mechanical stimulation (LMMS) is a relatively new technology which has shown to significantly modulate key physiological functions in the human body including bone mineralization, angiogenesis, and stem-cell differentiation.
- LMMS is applied through the feet, by standing on a platform oscillating at relatively high frequency.
- The mechanical signals are anabolic to the skeletal system by stimulating mesenchymal stem cell populations toward osteoblastogenesis.
- LMMS is non-invasive and non-pharmacologic with minimal risk for adverse events.

## JUVENT'S MICRO-IMPACT PLATFORM®: A WORLD LEADER IN LMMS TECHNOLOGY FOR HEALTHCARE AND SPORTS APPLICATIONS

- Juvent's Micro-Impact Platform is the result of \$45 million of research and development, which has culminated in over 20 patents worldwide.
- Its unique LMMS reflects an ideal combination of intelligent software, a high-resolution accelerometer, and a precision mechanism that optimizes a signal optimized for each user.
- Unlike whole body vibration (WBV) 'shakers' Juvent's Smart Technology provides precisely controlled micro-impacts by self-adjusting avoiding the risks of injury.

## OSTEOARTHRITIS (OA) OR DEGENERATIVE JOINT DISEASE

- OA or degenerative joint disease is the most common form of arthritis and characterized by degeneration of articular cartilage with proliferation and remodeling and breakdown of subchondral bone and synovium.
- Symptoms include stiffness, limpness, chronic pain and its prevalence markedly increased with age.
- Elderly patients with OA have more restricted activity and increased bed confinement, significantly affecting their quality of life and are at increased risk for co-morbidities.
- NSAID is the primary treatment modality but has serious side effects on cartilage morphogenesis, stomach, GI tract, liver and kidney.
- Adverse effects appear to be exacerbated in elderly patients- who are more prone to OA.
- Non-surgical and non-pharmacologic interventions are highly needed.



## LMMS MAY BE A NEW MEANS OF TREATING THE SYMPTOMS OF OSTEOARTHRITIS

- Numerous clinical studies have shown that LMMS improves pain, balance, gait quality, and inflammatory markers in elderly subjects with knee OA<sup>1</sup>.
- LMMS has been shown to decrease fatigue and pain levels, and to improve muscle strength in patients with fibromyalgia and to decrease pain levels in patients with knee osteoarthritis, as well as to increase strength and balance, in OA conditions.<sup>3,4,6,10</sup>
- Recent studies show that the addition of LMMS with squat exercise modulate T-cell-mediated immunity, minimizing or slowing disease progression in elderly patients with OA of the knee<sup>11</sup>.

### Literature Cited:

1. Zafar H, Alghadir A, Anwer S, Al-Eisa E. Therapeutic effects of whole-body vibration training in knee osteoarthritis: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2015 Aug;96(8):1525-32. doi: 10.1016/j.apmr.2015.03.010.
2. Pang MYC. Whole body vibration therapy in fracture prevention among adults with chronic disease. *World J Orthop* 2010; 1(1): 20-25 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v1/i1/20.htm> DOI: <http://dx.doi.org/10.5312/wjo.v1.i1.20>
3. Palmieri-Smith RM, Thomas AC, Karvonen-Gutierrez C, Sowers MF. Isometric quadriceps strength in women with mild, moderate, and severe knee osteoarthritis. *Am J Phys Med Rehabil* 2010; 89: 541-548
4. Trans T, Aaboe J, Henriksen M, Christensen R, Bliddal H, Lund H. Effect of whole body vibration exercise on muscle strength and proprioception in females with knee osteoarthritis. *Knee* 2009; 16: 256-261
5. Tsuji, J. Yoon, T. Aiba, A. Kanamori, T. Okura, K. Tanaka. Effects of whole-body vibration exercise on muscular strength and power, functional mobility and self-reported knee function in middle-aged and older Japanese women with knee pain. *Knee*, 21 (2014), pp. 1088–1095
6. Y.G. Park, Y.G., B.S. Kwon, J.W. Park, et al. Therapeutic effect of whole body vibration on chronic knee osteoarthritis. *Ann Rehabil Med*, 37 (2013), pp. 505–515
7. Simão, A.P., N.C. Avelar, R. Tossige-Gomes, et al. Functional performance and inflammatory cytokines after squat exercises and whole-body vibration in elderly individuals with knee osteoarthritis. *Arch Phys Med Rehabil*, 93 (2012), pp. 1692–1700
8. Avelar, N.C., A.P. Simão, R. Tossige-Gomes, et al. The effect of adding whole-body vibration to squat training on the functional performance and self-report of disease status in elderly patients with knee osteoarthritis: a randomized, controlled clinical study. *J Altern Complement Med*, 17 (2011), pp. 1149–1155
9. Tossige-Gomes R1, Avelar NC, Simão AP, Neves CD, Brito-Melo GE, Coimbra CC, Rocha-Vieira E, Lacerda AC.
10. Whole-body vibration decreases the proliferative response of TCD4(+) cells in elderly individuals with knee osteoarthritis. *Braz J Med Biol Res*. 2012 Dec;45(12):1262-8. Epub 2012 Sep 6.
11. Simão AP1, Avelar NC, Tossige-Gomes R, Neves CD, Mendonça VA, Miranda AS, Teixeira MM, Teixeira AL, Andrade AP, Coimbra CC, Lacerda AC. Functional performance and inflammatory cytokines after squat exercises and whole-body vibration in elderly individuals with knee osteoarthritis. *Arch Phys Med Rehabil*. 2012 Oct;93(10):1692-700. doi: 10.1016/j.apmr.2012.04.017. Epub 2012 Apr 27.



## RHEUMATOID ARTHRITIS (RA)

- Rheumatoid arthritis (RA) - an autoimmune condition - which manifests mainly in peripheral synovial joints result in chronic pain, joint destruction, and decreased functional ability.
- Osteoporosis and osteopenia are common in RA patients with rapid loss of bone.
- Patients with RA spend the majority of their day being sedentary resulting in poor bone mass.
- Exercise interventions in RA are not always feasible, specifically bone loading exercises which need to be dynamic in order to increase bone mass.
- LMMS is safe and requires minimal effort and movement.

## MECHANICAL STIMULATION AS AN ALTERNATIVE EFFECTIVE INTERVENTION FOR RHEUMATOID ARTHRITIS; A CLINICAL STUDY

- Functional ability is often impaired for people with rheumatoid arthritis (RA), rendering these patients highly sedentary.
- This study aimed to investigate the effects of mechanical stimulation therapy in patients with stable, established RA.
- Randomized trial of mechanical stimulation in 31 female patients with stable, established RA, with a control group that continued normal activities, and a treatment group that was given three months of mechanical stimulation therapy, consisting of 15 minutes of intermittent stimulation, 2 times per week.
- Functional ability assessed at baseline, three months and three months post-intervention and RA disease activity assessed at the same time points with the Clinical Disease Activity Index. Quality of life assessed with self-report fatigue and pain scores and physical activity profiles assessed with accelerometry.

### Key findings

- Functional ability significantly improved in the treatment group after the intervention (1.22 Vs 0.92).
- Hip BMD in the control group reduced (0.97 to 0.84 g.cm<sup>-2</sup>), but was not reduced in the treatment group (1.01 Vs 0.94 g.cm<sup>-2</sup>).
- There was no change in RA disease activity in either group.
- Fatigue levels were improved in the treatment group at follow-up but did not change in the control group at either follow-up time point.
- Ten-minute bouts of light to moderate physical activity were significantly reduced in the control group after the intervention and were preserved in the treatment group.
- Reduced fatigue and 'feeling well' – two important and relevant outcomes from the patient perspective in RA- were significantly improved.
- Overall, functional ability and quality of life has significantly improved by using mechanical stimulation in RA patients.

### Literature Cited:

1. Pioreschi A, Tikly M, McVeigh JA. A three month controlled intervention of intermittent whole body vibration designed to improve functional ability and attenuate bone loss in patients with rheumatoid arthritis. *BMC Musculoskelet Disord*. 2014. 29;15:403 doi: 10.1186/1471-2474-15-403 [PMC free article] [PubMed]
2. Pioreschi A1,2, Makda MA3, Tikly M3, McVeigh JA1. In Patients with Established RA, Positive Effects of a Randomised Three Month WBV Therapy Intervention on Functional Ability, Bone Mineral Density and Fatigue Are Sustained for up to Six Months. *PLoS One*. 2016 Apr 13;11(4):e0153470. doi: 10.1371/journal.pone.0153470. eCollection 2016.
3. Wang P, Yang X, Yang Y, Yang L, Zhou Y, Liu C, Reinhardt JD, He C. Effects of whole body vibration on pain, stiffness and physical functions in patients with knee osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil*. 2015 Oct;29(10):939-51. doi: 10.1177/0269215514564895. Epub 2014 Dec 18. Review.
4. JA McVeigh, A Pioreschi, I Avidon, T Oosthuysen Whole Body Vibration Increases Hip Bone Mineral Density in Well-Trained Cyclists. *JOURNAL OF GENERAL INTERNAL MEDICINE* 27, 244-244
5. A Pioreschi, T Oosthuysen, I Avidon, J McVeigh Whole Body Vibration Increases Hip Bone Mineral Density in Road Cyclists. *International journal of sports medicine*

### WILLIS-EKBOM SYNDROME OR RESTLESS LEG SYNDROME (TESTIMONIALS, CALCIUM REGULATION)



- Restless legs syndrome (RLS), a movement disorder, is a neurological perception characterized by unpleasant sensations in the legs and an uncontrollable, and irresistible, urge to move them. Most people with RLS have difficulty falling and staying asleep
  - 10 % of the U.S. population has RLS with high incidences in women. Childhood RLS is estimated to affect almost 1 million children, with one-third having moderate to severe symptoms.
  - RLS patients report that their job, personal relations, and activities of daily living are strongly affected as a result of their sleep deprivation and exhaustion. They are often unable to concentrate, impaired memory, or fail to accomplish everyday tasks. It also can make traveling difficult and can cause depression.
- People with RLS also experience a more common condition known as periodic limb movement of sleep (PLMS)- involuntary leg twitching or jerking movements during sleep causing awakening and severely disrupted sleep. PLMD may be a variant of RLS and thus respond to similar treatments.
  - RLS is related to a dysfunction in the brain's basal ganglia circuits, which results in involuntary movements. Individuals with Parkinson's disease often have RLS as well.
  - Certain drugs, alcohol and sleep deprivation aggravate RLS symptoms also may worsen in some individuals.

### Literature Cited:

1. Burbank F, Buchfuhrer MJ, Kopjar B. Sleep improvement for restless legs syndrome patients. Part I: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013, 3:1-10
2. Burbank F, Buchfuhrer MJ, Kopjar B. Improving sleep for patients with restless legs syndrome. Part II: meta-analysis of vibration therapy and drugs approved by the FDA for treatment of restless legs syndrome
3. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013, 3:11-22
4. Burbank F. Sleep improvement for restless legs syndrome patients. Part III: effect of treatment assignment belief on sleep improvement in restless legs syndrome patients. A mediation analysis. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013: 3:23-29
5. Burbank F. Sleep improvement for restless legs syndrome patients. Part IV: meta-analysis comparison of effect sizes of vibratory stimulation sham pads and placebo pills. 2014, 4:35-40



## WOUND HEALING, FRACTURE HEALING AND SKIN HEALTH

Chung SL1, Leung KS, Cheung WH. **Low-magnitude high-frequency vibration enhances gene expression related to callus formation, mineralization and remodeling during osteoporotic fracture healing in rats.** *J Orthop Res.* 2014 Dec;32(12):1572-9. doi: 10.1002/jor.22715. Epub 2014 Aug 17.

### Abstract

Low magnitude high-frequency vibration (LMHFV) has been shown to improve anabolic and osteogenic responses in osteoporotic intact bones and during osteoporotic fracture healing; however, the molecular response of LMHFV during osteoporotic fracture healing has not been investigated. It was hypothesized that LMHFV could improve osteoporotic fracture healing by regulating the expression of genes related to chondrogenesis (Col-2), osteogenesis (Col-1) and remodeling (receptor activator for nuclear factor- $\kappa$ B ligand (RANKL) and osteoprotegerin (OPG)). In this study, the effects of LMHFV on both osteoporotic and normal bone fracture healing were assessed by endpoint gene expressions, weekly radiographs, and histomorphometry at weeks 2, 4 and 8 post-treatment. LMHFV enhanced osteoporotic fracture healing by up-regulating the expression of chondrogenesis, osteogenesis- and remodeling-related genes (Col-2 at week 4 ( $p=0.008$ ), Col-1 at week 2 and 8 ( $p<0.001$  and  $p=0.008$ ) and RANKL/OPG at week 8 ( $p=0.045$ )). Osteoporotic bone had a higher response to LMHFV than normal bone and showed significantly better results as reflected by increased expression of Col-2 and Col-1 at week 2 ( $p<0.001$  for all), larger callus width at week 2 ( $p=0.001$ ), callus area at week 1 and 5 ( $p<0.05$  for all) and greater relative area of osseous tissue ( $p=0.002$ ) at week 8. This study helps to understand how LMHFV regulates gene expression of callus formation, mineralization, and remodeling during osteoporotic fracture healing.

Chow DH1, Leung KS, Qin L, Leung AH, Cheung WH. **Low-magnitude high-frequency vibration (LMHFV) enhances bone remodeling in osteoporotic rat femoral fracture healing.** *J Orthop Res.* 2011 May;29(5):746-52. doi: 10.1002/jor.21303

Low-magnitude high-frequency vibration (LMHFV) (35Hz, 0.3g) accelerates fracture healing by enhancing callus formation and mineralization for both normal and osteoporotic rats in our previous studies.<sup>1,2</sup> We hypothesized that LMHFV enhances fracture healing through bone remodeling. Ibandronate was used to suppress LMHFV-stimulated bone remodeling, and changes in remodeling were investigated to verify our hypothesis.

Closed femoral fractures were created in 80 osteoporotic female Sprague-Dawley rats. The rats were randomly assigned into a control (CG), LMHFV (VG) (20 min/day, 5 days/week), ibandronate (BG) (7  $\mu$ g/kg/week), or LMHFV + ibandronate (VBG) for a treatment duration of 2, 4, 6, or 8 weeks.

Blood taken from the femora was harvested for histological and radiological analyses. VG had the fastest drop in the callus area (CA) and width (CW), and bone volume to tissue volume ratio (BV/TV); whereas, a plateaued trend in BG and VBG was observed.

The fastest callus reduction, highest mineral apposition rate at week 6, and increased serum concentration of osteocalcin and TRAP5b in VG suggested enhanced remodeling. LMHFV partially reversed the inhibition of bone remodeling by ibandronate suggested LMHFV had an opposite effect on bone remodeling to ibandronate. In conclusion, LMHFV accelerated fracture healing by enhancing bone remodeling and the administration of ibandronate can impair this enhancement. LMHFV has great potential in improving fracture outcome clinically.

Cheung WH1, Chow SK, Sun MH, Qin L, Leung KS. **Low-intensity pulsed ultrasound accelerated callus formation, angiogenesis and callus remodeling in osteoporotic fracture healing.** *Ultrasound Med Biol.* 2011 Feb;37(2):231-8. doi: 10.1016/j.ultrasmedbio.2010.11.016.

Osteoporotic fracture is a critical medico-social challenge leading to burdens in health care costs and hospital bed stays. Low-intensity pulsed ultrasound (LIPUS) was reported to accelerate normal fracture; however, its effect on osteoporotic fracture has not been previously addressed. We hypothesize that LIPUS can accelerate osteoporotic fracture healing and up-regulate the expression in the osteogenesis-, remodeling- and angiogenesis-related genes. An ovariectomy-induced osteoporotic fracture rat model was used to investigate the effects of LIPUS. Fractured rats were assigned to LIPUS or control group and healing was assessed by gene expression quantification, radiographic callus morphometry, and histomorphometry.

In the LIPUS group, Col-1 and bone morphogenetic protein-2 were up-regulated at earlier time points of week 2 to week 4 post-fracture; vascular endothelial growth factor was found to be up-regulated at week 4 to week 8; osteoprotegerin was up-regulated at week 2 post-fracture, followed by the surge of RANKL expression. Callus width and area measurements showed higher callus formation at weeks 2-4 in the LIPUS group and more rapid drop at weeks 6-8. Histomorphometry showed enhanced endochondral ossification in the callus at weeks 2-4, and lower at week 8. We conclude that LIPUS can accelerate osteoporotic fracture healing by improving callus formation, angiogenesis and callus remodeling.

*Shi HF1, Cheung WH, Qin L, Leung AH, Leung KS. **Low-magnitude high-frequency vibration treatment augments fracture healing in ovariectomy-induced osteoporotic bone.** Bone. 2010 May;46(5):1299-305. doi: 10.1016/j.bone.2009.11.028.*

Fracture healing is impaired in osteoporotic bone. Low-magnitude high-frequency vibration (LMHFV) has recently been proven to be osteogenic in osteoporotic intact bone. Our previous study found that LMHFV significantly enhanced fracture healing in adult rats.

This study was designed to explore whether LMHFV was able to improve fracture healing in osteoporotic bone by enhancing callus formation, remodeling, and mineralization, and to compare with age-matched nonosteoporotic ones. Nine-month-old ovariectomy (OVX)-induced osteoporotic rats were randomized into control (OVX-C) or vibration group (OVX-V); age-matched sham-operated rats were assigned into control (Sham-C) or vibration group (Sham-V). LMHFV (35 Hz, 0.3 g) was given 20 min/day and 5days/week to the treatment groups, while the sham treatment given to the control groups.

Weekly radiographs and endpoint micro-CT, histomorphometry, and mechanical properties were evaluated at 2, 4, and 8 weeks post-treatment. Results confirmed that the fracture healing in OVX-C was significantly inferior to that in Sham-C. LMHFV was shown to be effective in promoting the fracture healing in OVX group in all measured parameters, particularly in the early phases of healing, with the outcomes comparable to that of age-matched normal fracture healing. Callus formation, mineralization, and remodeling were enhanced by 25-30%, with a 70% increase in energy to failure than OVX-C. However, Sham-V was found to have lesser fracture healing enhancement, with a significant improvement in the callus area only on week 2 and 3 than Sham-C, suggesting non-OVX aged bones were less sensitive to mechanical loading. The findings of this study indicate a basis that proceeding to clinical trials is the next step to evaluate the efficacy of LMHFV on osteoporotic fracture healing.

*Wu SH1, Zhong ZM, Chen JT. **Low-magnitude high-frequency vibration inhibits RANKL-induced osteoclast differentiation of RAW264.7 cells.** Int J Med Sci. 2012;9(9):801-7. doi: 10.7150/ijms.4838.*

Osteoclasts are the key participants in the regulation of bone mass. Low-magnitude high-frequency vibration (LMHFV) has been found to be anabolic to the bone in vivo. This study aimed to investigate the effect of LMHFV on osteoclast differentiation in vitro. Murine monocyte cell line RAW264.7 cells in the presence of receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) were treated with or without LMHFV at 45 Hz (0.3 g) for 15 min day<sup>-1</sup>. Tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells (MNCs) and actin ring formation were evaluated. Expression of the osteoclast-specific genes, such as cathepsin K, matrix metalloproteinase-9 (MMP-9) and TRAP, were analyzed using real time-PCR. c-Fos, an osteoclast-specific transcription factor, was determined using Western blot. We found that LMHFV significantly decreased the number of RANKL-induced TRAP-positive MNCs ( $P < 0.01$ ), and inhibited the actin ring formation. The mRNA expression of the cathepsin K, MMP-9 and TRAP were down-regulated by LMHFV intervention (all  $P < 0.001$ ). Furthermore, LMHFV also inhibited the expression of the c-Fos protein in the RANKL-treated RAW264.7 cells ( $P < 0.05$ ). Our results suggest that LMHFV can inhibit the RANKL-induced osteoclast differentiation of RAW264.7 cells, which give some new insight into the anabolic effects of LMHFV on bone.

*Leung KS1, Shi HF, Cheung WH, Qin L, Ng WK, Tam KF, Tang N. **Low-magnitude high-frequency vibration accelerates callus formation, mineralization, and fracture healing in rats.** J Orthop Res. 2009 Apr;27(4):458-65. doi: 10.1002/jor.20753.*

Fracture healing is a biological regenerative process that follows a well-orchestrated sequence. Most healing is uneventful, and the enhancement of normal fracture healing is not commonly done, although it is clinically significant in the recovery and regain of functions after fracture.

This study investigated the osteogenic effect of low-magnitude high-frequency vibration (LMHFV, 35 Hz, 0.3 g) on the enhancement of fracture healing in rats with closed femoral shaft fracture by comparing with sham-treated control. Assessments with plain radiography, micro-CT as well as histomorphometry showed that the amount of callus was significantly larger ( $p = 0.001$  for callus area, 2 weeks posttreatment); the remodeling of the callus into mature bone was significantly faster ( $p = 0.039$ , 4 weeks posttreatment) in the treatment group.

The mechanical strength of the healed fracture in the treatment group at 4 weeks was significantly higher ( $p < 0.001$ ). The results showed the acceleration of callus formation, mineralization, and fracture healing in the treatment group. It is concluded that LMHFV enhances healing in the closed femoral shaft fracture in rats. The potential clinical advantages shall be confirmed in the subsequent clinical trials.

*Wei FY1, Chow SK, Leung KS, Qin J, Guo A, Yu OL, Li G, Cheung WH. **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.*

Low-magnitude high-frequency vibration (LMHFV) has been proven to promote osteoporotic fracture healing. Mechanical stimulation was reported to enhance SDF-1/CXCR4 signalling in mesenchymal stem cells (MSCs). We hypothesized that LMHFV promoted osteoporotic fracture healing by enhancing MSC migration through the SDF-1/CXCR4 pathway.

152 ovariectomized SD-rats received closed femoral fracture in groups of vibration+MSC (VMG) (20 min/d, 5 d/week), vibration+MSC+AMD3100 (VMAG; AMD, a CXCR4 inhibitor) (1 mg/kg/d, intraperitoneal), MSC (MG) ( $1 \times 10^6$  MSC, intracardiac) or control (CG) for a treatment duration of 2, 4 or 8 weeks.

MSC migration was evaluated by ex-vivo green fluorescent protein signal in the callus, and fracture healing was examined by weekly radiographs, endpoint computed tomography and mechanical test. At week-2 and week-4, ex-vivo callus GFP intensity of VMG was significantly higher than other groups ( $p < 0.05$ ). From week-2 to week-3, both callus width and callus area in VMG were significantly larger; and from week-7 to week-8, smaller than other groups ( $p < 0.05$ ). At week-8, high-density bone volume fraction, bone volume fraction, bone mineral density and stiffness in VMG were significantly higher than other three groups ( $p < 0.05$ ). This study demonstrated that LMHFV promoted MSC migration and fracture healing in osteoporotic rats. This effect was attenuated by CXCR4 inhibitor, providing strong evidence that SDF-1-mediated MSC migration was one of the important mechanisms through which LMHFV enhanced fracture healing.

## **ADIPOGENESIS AND WEIGHT LOSS - (ANIMAL STUDY)**

- Bone metabolism may also exert an endocrine regulation of glucose homeostasis and body weight, potentially making bone an important determinant of type 2 diabetes. In children, physical inactivity and obesity have been linked to many health issues, including poor skeletal development
- Dietary and exercise interventions have improved insulin sensitivity and osteocalcin 5, 6; however, changes in osteocalcin levels and insulin sensitivity are not always related
- Obesity, a global pandemic that debilitates millions of people and burdens society with tens of billions of dollars in health care costs, is deterred by exercise. Although it is presumed that the more strenuous a physical challenge the more effective it will be in the suppression of adiposity, here it is shown that 15 weeks of brief, daily exposure to high-frequency mechanical signals, induced at a magnitude well below that which would arise during walking, inhibited adipogenesis by 27% in C57BL/6J mice. The mechanical signal also reduced key risk factors in the onset of type II diabetes, nonesterified free fatty acid and triglyceride content in the liver, by 43% and 39%, respectively. Over nine weeks, these same signals suppressed fat production by 22% in the C3H.B6–6T congenic mouse strain that exhibits accelerated age-related changes in body composition.
- Metabolic disease such as diabetes mellitus and obesity is emerging as a major public health problem and have a high impact on individual quality of life for those affected, as well as a huge burden on national healthcare costs, contributing substantially to the billion annual healthcare expenditures.
- Metabolic diseases such as diabetes, obesity, and hypertension are serious health issues. Among them, diabetes mellitus is emerging as a significant public health problem in the US in parallel with worldwide diabetes pandemic.
- WBV interventions provided a significant reduction of 25.7 ml/dl (95% CI:-45.3 to -6.1; I2: 19%) in 12 hours fasting blood glucose compared with no intervention.
- Improvements in glycated hemoglobin, cardiovascular risk factors, and physical and functional capacity were found only at 12 weeks after WBV intervention in comparison with no intervention.
- WBV combined with exercise seems to improve glycemic control slightly in patients with T2DM in an exposure-dependent way.

### **Literature Cited:**

1. Jing D, Luo E, Cai J, Tong S, Zhai M, Shen G, Wang X, Luo Z. Mechanical Vibration Mitigates the Decrease of Bone Quantity and Bone Quality of Leptin Receptor-Deficient Db/Db Mice by Promoting Bone Formation and Inhibiting Bone Resorption. *J Bone Miner Res.* 2016 Mar 17. doi: 10.1002/jbmr.2837.
2. C. T. Rubin, E. Capilla, Y. K. Luu, B. Busa, H. Crawford, D. J. Nolan, V. Mittal, C. J. Rosen, J. E. Pessin, and S. Judex. Adipogenesis is inhibited by brief, daily exposure to high-frequency, extremely low-magnitude mechanical signals. *Proc Natl Acad Sci U S A.* 2007 Nov 6;104(45):17879-84.
3. Robinson CC, Barreto RP, Sbruzzi G, Plentz RD. The effects of whole body vibration in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Braz J Phys Ther.* 2016 Feb;20(1):4-14. doi: 10.1590/bjpt-rbf.2014.0133.



## INSULIN MANAGEMENT - OSTEOCALCIN LEVELS

As of 2010, over 285 million people worldwide were suffering from type 2 diabetes, which is a metabolic disorder characterized by high blood glucose as a result of insulin resistance.

### **Literature Cited:**

1. Li M, Wu W2 Tan L, Mu D, Zhu D, Wang J3 Zhao B. Low-magnitude mechanical vibration regulates expression of osteogenic proteins in ovariectomized rats. *Biochem Biophys Res Commun*. 2015 Sep 25;465(3):344-8. doi: 10.1016/j.bbrc.2015.07.154
2. Wehrle E1, Liedert A, Heilmann A1, Wehner T, Bindl R1, Fischer L1, Haffner-Luntzer M1, Jakob F2, Schinke T3, Amling M3, Ignatius A4. The impact of low-magnitude high-frequency vibration on fracture healing is profoundly influenced by the oestrogen status in mice. *Dis Model Mech*. 2015 Jan;8(1):93-104. doi: 10.1242/dmm.018622. Epub 2014 Nov 7.
3. Jing D1,2, Luo E2, Cai J3, Tong S2, Zhai M2, Shen G2, Wang X4, Luo Z1. Mechanical Vibration Mitigates the Decrease of Bone Quantity and Bone Quality of Leptin Receptor-Deficient Db/Db Mice by Promoting Bone Formation and Inhibiting Bone Resorption. *J Bone Miner Res*. 2016 Mar 17. doi: 10.1002/jbmr.2837.
4. Jing D, Luo E, Cai J, Tong S, Zhai M, Shen G, Wang X, Luo Z. Mechanical Vibration Mitigates the Decrease of Bone Quantity and Bone Quality of Leptin Receptor-Deficient Db/Db Mice by Promoting Bone Formation and Inhibiting Bone Resorption. *J Bone Miner Res*. 2016 Mar 17. doi: 10.1002/jbmr.2837.

## CROHN'S DISEASE

- *Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract associated with defective innate immune regulation.*
- *Children and adolescents with CD have multiple risk factors for impaired bone accrual, including poor growth, delayed puberty, malnutrition, cachexia, decreased physical activity, chronic inflammation, and glucocorticoid therapy.*
- *Impaired bone accrual in childhood inflammatory diseases poses an immediate fracture risk, and low peak bone mass may result in lifelong skeletal fragility*
- *Children with CD and documented substantial deficits in tibia trabecular bone mineral density (BMD), cortical dimensions, and muscle mass at diagnosis.*

## LMMS AS AN ALTERNATIVE EFFECTIVE INTERVENTION FOR CROHN'S DISEASE; A CLINICAL STUDY

- 12-month randomized, double-blind placebo-controlled trial of 10 minutes daily exposure to LMMS (30 Hz frequency, 0.3g peak-to-peak acceleration). The primary outcomes were tibia trabecular BMD and cortical area by peripheral quantitative CT (pQCT) and vertebral trabecular BMD by QCT; additional outcomes included dual-energy X-ray absorptiometry (DXA) whole body, hip and spine BMD, and lean leg mass.
- Results were expressed as sex-specific Z-scores relative to age. CD participants, ages 8 to 21 years with tibia trabecular BMD <25th percentile for age, were eligible and received daily cholecalciferol (800 IU) and calcium (1000 mg).
- In total, 138 enrolled (48% male), and 121 (61 actives, 60 placebos) completed the 12-month trial. Median adherence measured with an electronic monitor was 79% and did not differ between arms.
- By intention-to-treat analysis, LMMS had no significant effect on pQCT or DXA outcomes. The mean change in spine QCT trabecular BMD Z-score was +0.22 in the active arm and -0.02 in the placebo arm (difference in change 0.24 [95% CI 0.04, 0.44]; p=0.02).
- Among those with >50% adherence, the effect was 0.38 (95% CI 0.17, 0.58, p < 0.0005). Within the active arm, each 10% greater adherence was associated with a 0.06 (95% CI 0.01, 1.17, p=0.03) more significant increase in spine QCT BMD Z-score.

- Treatment response did not vary according to baseline body mass index (BMI) Z-score, pubertal status, CD severity, or concurrent glucocorticoid or biologic medications.
- In all participants combined, height, pQCT trabecular BMD, and cortical area and DXA outcomes improved significantly.
- In conclusion, LMMS was associated with increases in vertebral trabecular BMD by QCT

**Literature Cited:**

Leonard MB1, Shults J2, Long J1, Baldassano RN3, Brown JK4, Hommel K5, Zemel BS3, Mahboubi S3, Howard Whitehead K3, Herskovitz R3, Lee D5, Rausch J, Rubin CT7. Effect of Low Magnitude Mechanical Stimuli on Bone Density and Structure in Pediatric Crohn's Disease: A Randomized Placebo-Controlled Trial. *J Bone Miner Res.* 2016 Jun;31(6):1177-88. doi: 10.1002/jbmr.2799.

**THALASSEMIA DISEASE**

- Patients with Thalassemia have many risk factors that adversely affect bone mass including ineffective erythropoiesis which leads to bone marrow hyperplasia and cortical thinning [1], poor growth, endocrine, and growth hormone deficiencies [2], diabetes [3,4], and decreased circulating vitamin D levels [5].
- Although many patients are small for age, bone mineral deficits are not completely explained by growth and lean mass deficits [1,6,]. Bone resorption is elevated in adult Thal compared to reference data, whereas reduced bone formation is a key component leading to the bone mineral deficits observed in young Thal patients [1,7]. Bone histomorphometry from iliac crest biopsies in children with Thal reveals impaired bone matrix, defective mineralization, and reduced formation rate, which is associated with iron deposits within the bone.
- Despite the pervasiveness of low bone mass in Thal, there are few therapies available to young patients [2,9]; most are treated for hypogonadism through hormonal replacement and encouraged to take calcium and vitamin D supplements. Despite these efforts, the majority of patients continue to lose bone as they age, as much as 1 to 2% per year starting in the 3rd decade of life [10]. The primary pharmacologic treatment available to patients is bisphosphonate therapy aimed at reducing bone loss [8]. Alternative therapies focused on increasing bone formation have not been evaluated. Physical activity can increase bone mineral acquisition [11]; however, some cardiovascular exercises are not tolerated in Thal patients with cardiac complications. Recent advances in the field have shown that low magnitude (0.3 g), high frequency (20–90 Hz) mechanical stimulation can promote bone formation at a magnitude well below that which is reached from walking alone [12–14]. Whole body vibration (WBV) therapy has also been shown to improve strength and inhibit adipogenesis [14–16]. Seven studies have been published using WBV in postmenopausal women [17,18], young females with low bone mass [19,20], and children with cerebral palsy [21–23].

**Literature Cited:**

1. Li M, Wu W2 Tan L, Mu D, Zhu D, Wang J3 Zhao B. Low-magnitude mechanical vibration regulates expression of osteogenic proteins in ovariectomized rats. *Biochem Biophys Res Commun.* 2015 Sep 25;465(3):344-8. doi: 10.1016/j.bbrc.2015.07.154
2. Gusi N, Raimundo A, Leal A. Low frequency vibratory exercise reduces the risk of bone fracture more than walking: A randomized controlled trial. *BMC Musculoskel Disord.* 2006;30:87–92. [PMC free article] [PubMed]
3. Bogaerts A, Delecluse C, Boonen S, et al. Changes in balance functional performance and fall risk following whole body vibration training and vitamin D supplementation in institutionalized elderly women. A 6 month randomized controlled trial. *Gait Posture.*2011;33:466–472. [PubMed]
4. Rubin CT, Capilla E, Luu YK, et al. Adipogenesis is inhibited by brief, daily exposure to high-frequency, extremely low-magnitude mechanical signals. *Proc Nat Acad Sci.*2007;104:17879–17884. [PMC free article] [PubMed]
5. Ward K, Alsop C, Caulton J, et al. Low magnitude mechanical loading is osteogenic in children with disabling conditions. *J Bone Min Res.* 2004;19:360–369. [PubMed]
6. Wren TAL, Lee DC, Hara R, et al. Effect of high-frequency, low magnitude vibration on bone and muscle in children with cerebral palsy. *J Ped Ortho.* 2010;30:732–738.[PMC free article] [PubMed]
7. Reyes ML, Hernandez M, Holmgren LJ, et al. High frequency, low intensity vibrations increase bone mass and muscle strength in upper limbs, improving autonomy in disabled children. *J Bone Min Res.* 2011;26:1759–1766. [PubMed]