

# The Efficacy of Low-intensity Vibration to Improve Bone Health in Patients with End-stage Renal Disease Is Highly Dependent on Compliance and Muscle Response

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**Rational and Objectives:** Low intensity vibration (LIV) may represent a nondrug strategy to mitigate bone deficits in patients with end-stage renal disease.

**Materials and Methods:** Thirty end-stage renal patients on maintenance hemodialysis were randomized to stand for 20 minutes each day on either an active or placebo LIV device. Analysis at baseline and completion of 6-month intervention included magnetic resonance imaging (tibia and fibula stiffness; trabecular thickness, number, separation, bone volume fraction, plate-to-rod ratio; and cortical bone porosity), dual-energy X-ray absorptiometry (hip and spine bone mineral density [BMD]), and peripheral quantitative computed tomography (tibia trabecular and cortical BMD; calf muscle cross-sectional area).

**Results:** Intention-to-treat analysis did not show any significant changes in outcomes associated with LIV. Subjects using the active device and with greater than the median adherence (70%) demonstrated an increase in distal tibia stiffness (5.3%), trabecular number (1.7%), BMD (2.3%), and plate-to-rod ratio (6.5%), and a decrease in trabecular separation (−1.8%). Changes in calf muscle cross-sectional area were associated with changes in distal tibia stiffness ( $R = 0.85$ ), trabecular bone volume/total volume ( $R = 0.91$ ), number ( $R = 0.92$ ), and separation ( $R = -0.94$ ) in the active group but not in the placebo group. Baseline parathyroid hormone levels were positively associated with increased cortical bone porosity over the 6-month study period in the placebo group ( $R = 0.55$ ) but not in the active group ( $R = 0.01$ ). No changes were observed in the nondistal tibia locations for either group except a decrease in hip BMD in the placebo group (−1.7%).

**Conclusion:** Outcomes and adherence thresholds identified from this pilot study could guide future longitudinal studies involving vibration therapy.

**Key Words:** Vibration therapy; renal disease; MRI; bone; muscle.

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## INTRODUCTION

Renal osteodystrophy is a multifactorial and pervasive disorder of bone and mineral metabolism that parallels chronic kidney disease. This pernicious disease reduces bone quantity, disrupts bone turnover, and compromises mineralization processes, resulting in a skeleton highly

susceptible to fracture (1). This higher susceptibility to fracture is based on several factors. For one, elevated expression of the hormone fibroblast growth factor 23 in osteocytes during the early course of chronic kidney disease plays a critical role in the progression of abnormal mineral ion homeostasis by decreasing 1,25(OH)<sub>2</sub> vitamin D and ultimately impairing intestinal calcium absorption and increasing serum parathyroid hormone (PTH) (2). The overall relative risk for hip fracture has been estimated to be about 4.4 times greater for patients on dialysis as compared to people of the same sex in the general population, and mortality risk following fractures are markedly greater in end-stage renal disease patients compared to healthy adults (3–5).

The clinical effectiveness of osteoporosis therapies, such as phosphate binders, calcium, vitamin D, and conventional antiresorptive drugs to prevent fractures in end-stage renal disease has not been well established (6–12). To avoid adding yet another drug to their daily intake, it would be useful to

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improve the bone health of these patients by nonpharmacologic means. Recent studies have suggested that whole-body vibration may have a therapeutic role to play in improving bone health, particularly for individuals who are unable to tolerate exercise (13). In a 1-year study of adult female sheep, a 20-minute exposure each day to 30 Hz and 0.3g (where  $g$  = Earth's gravitational acceleration, or  $9.8\text{m/s}^2$ ) stimulation resulted in a 30% increase in trabecular bone mineral density (BMD) of the distal femur (14). In a follow-up study, finite element modeling was used to show that the anabolic response yields reduction in apparent strain magnitude in the trabeculae as well as produces a structure that is stiffer and less prone to fracture for a given load (8).

Small-scale clinical trials using these extremely low-intensity mechanical signals suggest an anabolic response in weight-bearing regions of the skeleton, with efficacy strongly correlated to compliance (15–18). For example, in a study recently published on the use of low-intensity vibration on children with Crohn disease, every decadal increase in adherence was associated with a 0.06 ( $P = .03$ ) greater increase in spine quantitative computed tomography (QCT) BMD Z-score (19). Importantly, in studies ranging from child cancer survivors (20) to the frail elderly (21), no serious adverse events have been reported. Delivered using vibration, the resulting low-intensity mechanical signals are intended to mimic the spectral content of muscle contractibility and result in deformation of bone of less than 10 microstrain (22), 200 times below the peak strains that are generated in the skeleton during strenuous activity (23). Although the optimal magnitude, frequency, and duration of such mechanical signals is not known, limiting exposure to a brief time and low intensity limits the risk of deleterious consequences of higher-magnitude vibrations, as defined by the International Organization for Standardization (ISO-2631) (24).

Despite the anabolic potential of vibration therapy, the underlying mechanisms of action are not well understood. According to one theory, mechanical stimulation causes activation of the musculature resulting in mechanotransduction of strains within bone, mimicking mechanical signals typically generated by postural muscle contractions or low-intensity activities such as walking (14,22,25). Another hypothesis is that mechanical stimulation signals are amplified within the bone tissue by stress-generated increase in fluid flow resulting from direct bone stimulation, thereby activating osteocytes, which act as mechanosensors to mediate the skeleton's response (26,27). However, there is also considerable evidence that suggests the vibrations cause larger displacements in cell nuclei than fluid shear, indicating the mechanism of action is more likely due to the mechanical coupling between these oscillating cell nuclei and the cytoskeleton, which ultimately induces actin remodeling and reduces bone resorption (6,28,29).

The primary goal of this study was to investigate the potential and feasibility of daily exposure to low-intensity vibration as a nonpharmacologic means to treat skeletal deficits in end-stage renal disease patients. A secondary goal was to investigate

the effect of muscle–bone interaction and PTH on bone response to mechanical stimulation.

## MATERIALS AND METHODS

Written, informed consent was obtained from all screened subjects. Thirty ambulatory end-stage renal disease patients (aged 21–65 years) on maintenance hemodialysis were recruited for this study from a single dialysis center. Maintenance hemodialysis patients in the 21- to 65-year age range were eligible for the study. Exclusion criteria included serious comorbidities (active malignancy or a history of myocardial infarction, congestive heart failure III–IV stage, cerebrovascular disease, liver failure, or neuropathy), pregnancy, a history of a fall within the prior 6 months, hip fracture or hip replacement, lower extremity amputation, anticipated living-donor transplantation or relocation within the coming 6 months, and difficulty in ambulation, defined as difficulty climbing two flights of stairs or walking three blocks. This 6-month, prospective, double-blinded, randomized, case controlled pilot study was approved by the authors' institutional review board and complied with Health Insurance Portability and Accountability Act guidelines.

### Randomization

Participants were randomized 1:1 to either an active or placebo low-intensity vibration device designed for home use. To mask the active/placebo status of the devices, all devices were equipped with a speaker that emitted a 500-Hz audible tone. The research coordinator who performed the randomization and instructed the participants in the use of the device was not involved in assessment of study outcomes. All other investigators were blinded to device assignment.

### Intervention

The active device oscillates in a vertical direction, at 30 Hz and 0.3g, an acceleration that requires a displacement of approximately  $90\text{ }\mu\text{m}$  (14). An accelerometer fixed to the top platen provides a closed-loop feedback signal to retain intensity values regardless of body weight or shifts in posture. The placebo device is identical in appearance, but the actuator is not active. All participants were asked to stand in a relaxed position (knees neither locked nor bent) and in bare or stocking feet on the platform for 20 minutes each day over a 6-month period (Fig 1). At these signal parameters and in relaxed stance, approximately 70%–80% of the mechanical information delivered to the plantar surface of the foot is transmitted to the hip and spine (30). An electronic compliance monitoring system within the device recorded the date, time, and duration of each use through the 6-month trial. At the end of the trial, the devices were returned to the study center and adherence data downloaded.

Self-reported intentional physical activity was recorded as the number of minutes in a typical day during the intervention

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