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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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Abstract

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

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interest: CTR has several issued patents relative to the use of mechanical signals to suppress bone fragility.

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.

Keywords

Vibration therapy; renal disease; MRI; bone; muscle

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 $1,25(\text{OH})_2$ 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 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 9.8m/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 μm (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 period participants were involved in intentional exercise, defined as walking for exercise, dancing, sports (team, dual, or individual), or conditioning (moderate or heavy). Physical activity data were obtained retrospectively at study visits instead through daily physical activity logs.

Outcome Measures

Magnetic resonance imaging (MRI), peripheral quantitative computed tomography (pQCT), and dual-energy X-ray absorptiometry (DXA) scans were obtained at baseline and completion of the 6-month intervention. Tibia and fibula were chosen as load-bearing and non-load-bearing bone, respectively, for MRI and pQCT because of the proximity to the site of the stimulus and for being on the direct transmission path of the vibrations.

MRI Acquisition

Participants were examined on a 1.5 Tesla whole-body MRI scanner (Siemens Sonata, Erlangen, Germany) in feet-first supine position. Using a custom-designed two-channel surface coil, a $70 \times 64 \times 13 \text{ mm}^3$ region (with the third dimension being along bone's axial direction) of the distal tibia and fibula metaphysis (3% site) were imaged with a fast large-angle spin echo pulse sequence (Fig 2) (31). Sequence parameters were flip angle of 140° , TR/TE 80 ms/11.8 ms (60% fractional-echo acquisition), 16.67-kHz bandwidth, and $137 \times 137 \times 410 \mu\text{m}^3$ voxel size in 15 minutes and 23 seconds. The diaphysis was imaged at the 38% site using a lower extremity coil provided by the scanner manufacturer. Imaging parameters for the axial fast spin-echo sequence were: TR/TE = 5s/16 ms, echo train length = 8, pixel size = 0.479 mm, field of view = $120 \times 120 \text{ mm}^2$, slice thickness = 2 mm, slice spacing = 7 mm, and number of slices = 30.

MRI-based Analysis

Co-registered trans-axial regions were extracted from the images acquired during the baseline and follow-up scans, corresponding to 8-mm and 42-mm thickness in the metaphysis and diaphysis, respectively (32). Using a custom-designed operator-guided segmentation algorithm, the cortical and trabecular compartments were extracted for analysis by delineating the endosteal and periosteal boundaries (33). Trabecular bone-

volume fraction (i.e., bone volume/total volume [BV/TV]) at the distal sites was calculated as the average of the voxel bone-volume fraction in the trabecular bone region. Trabecular thickness (Tb.Th) was computed using a fuzzy distance transform algorithm (34). Trabecular number (Tb.N) and trabecular separation (Tb.Sp) were computed as $(BV/TV)/Tb.Th$ and $Tb.Th/(BV/TV) - Tb.Th$, respectively (35). To describe the relative plate vs rod likeness of trabeculae, plate-to-rod ratio was also computed (36). Whole cross-section axial stiffness was computed using linear finite element analysis (33,37). Cortical porosity at the tibial diaphysis was computed as $(1 - BV/TV) \times 100\%$ at each voxel, averaged over the entire cortical bone region. The in vivo coefficient of variation for MRI measures has been previously shown to be 0.87%–3.02% (38–40).

DXA

DXA (Delphi/Discovery Densitometer, Hologic, Inc., Bedford, MA) scans were obtained in the array mode using standard positioning techniques. Posteroanterior lumbar spine (L1–L4) and left total-hip areal BMD (g/cm^2) were measured. The DXA instrument was calibrated using a hydroxyapatite spine phantom daily and a whole body phantom three times per week. The coefficient of variation for in vitro phantom scans and in vivo spine BMD scans are <1% at our institution (41).

pQCT

Bone density in the left tibia was obtained by pQCT (Stratec XCT 2000 12-detector unit, Orthometrix, Inc., Pforzheim, Germany) with a voxel size of 0.4 mm, slice thickness of 2.3 mm, and scan speed of 25 mm/s. All scans were analyzed with the Stratec software version 6.00 (42). At the 3% metaphyseal and 38% diaphyseal sites, scans were analyzed for trabecular and cortical volumetric BMD (mg/cm^3), respectively, whereas at the 66% site, scans were analyzed for calf muscle cross-sectional area (CSA). Quality control was monitored daily using a hydroxyapatite phantom. The in vivo coefficient of variation ranged from 0.5% to 1.6% for pQCT measures (43).

Outcome Analyses

Intention-to-treat analysis used data from all participants, regardless of adherence to either the active or placebo protocols. Post hoc analyses were performed to determine the role of compliance on any of the bone outcomes. In such cases, iterative processing was used to determine if there was a duration threshold for efficacy (15), or if there was a linear correlation such that better adherence improved bone outcomes. In post hoc analyses, outcomes relative to gender, disease state, and intentional physical activity were also tested.

Statistical Analysis

Changes in outcome parameters between baseline and follow-up were assessed using paired two-sided Student *t* tests when data were normally distributed. Otherwise, nonparametric Wilcoxon signed-rank tests were performed. Correlations among parameters were evaluated using the Pearson correlation coefficients when data were normally distributed and Spearman correlation when data were not normally distributed. Differences from baseline to follow-up in outcome variables between the active and placebo groups were evaluated via

unpaired t tests. Within-group temporal changes in parameters were calculated as percent changes and tested using a two-tailed t test or Wilcoxon signed-rank test to find mean differences from zero. All analyses were performed using JMP Discovery Software, Version 12.0 (SAS Institute, Inc., Cary, NC), with $P < .05$ indicating statistical significance.

RESULTS

Participant Characteristics

Participant characteristics for each group are listed in Table 1. One subject assigned to the active group withdrew from the study after 33 days because of a broken leg secondary to a fall, unrelated to the device use, and no follow-up data were obtained. The two groups did not significantly differ in intentional physical activity levels ($P = .88$) or medication use during the 6-month intervention. At baseline, there was no statistically significant difference in any of the bone parameters ($P > .13$) or calf muscle CSA ($P = .70$) measured between the active and placebo groups. Furthermore, distal tibia magnetic resonance images revealed visible abnormalities in the marrow region in two participants in the placebo group, including severely disconnected trabecular bone network, thinned cortical bone, and marrow fibrosis (Fig 3), which are not typically found in healthy individuals.

Adherence to Daily Device Use

The average level of adherence over the entire 6-month study period ranged between 0% and 100% (median 70%) across participants (Fig 4). Compliance was not significantly different between the active and placebo groups ($P = .60$). Seven participants had extremely poor adherence ($12\% \pm 13\%$), for reasons including never turning on the device, leaving the device with another person, relocating, or being too busy to adhere. No adverse events related to the device use were reported. There was no evidence that the participants knew they were on an active or placebo device.

Intention-to-Treat and Post Hoc Analyses

Intention-to-treat analysis showed no significant effect of 6 months of active vibration therapy on any of the measured parameters as compared to the placebo group (Table 2). Post hoc analysis using the median adherence in the active arm (70%) as the mechanical stimulation exposure threshold showed an increase in distal tibia stiffness (5.3%, $P = .022$), trabecular density (2.3%, $P = .034$), and plate-to-rod ratio (6.5%, $P = .004$) (Table 3). Furthermore, the temporal changes in tibia parameters were associated with adherence, particularly in participants with high exposure to mechanical stimulation (Table 4). Neither intention-to-treat nor post hoc analyses showed any significant changes in DXA bone measures at the hip and spine, except for a decrease in hip BMD (1.7%, $P = .0049$) in the placebo group, nor in the pQCT calf muscle CSA. There was no significant association between changes in bone parameters and end-stage renal disease duration, dialysis duration, gender, or intentional physical activity level.

Muscle-Bone Interaction

Post hoc analysis showed strong correlations between changes in calf muscle CSA and changes in bone parameters of the distal tibia in the active group (Table 5). No such

correlations were observed in the placebo group. At baseline, calf muscle CSA was significantly correlated with the BMD of the hip ($R = 0.58$, $P = .0017$) and spine ($R = 0.55$, $P = .0034$) but not with other parameters.

Effect of PTH on Cortical Bone

In the placebo group, baseline PTH levels were positively associated with the increases in cortical bone porosity over the subsequent 6-month study period ($R = 0.55$, $P = .039$). In contrast, porosity did not increase in the active group, regardless of baseline PTH levels ($R = 0.01$, $P = .96$). Changes in cortical bone density were negatively associated with baseline PTH levels independent of active or placebo usage ($R = -0.65$, $P = .0004$). Changes in other parameters were not significantly associated with baseline PTH values.

Location Dependence of Mechanical Stimulation Effect

In the distal fibula, no changes in any outcome variables were observed between the two time points, or between groups, even in post hoc analysis involving adherence. This is in contrast to the outcomes observed in the distal tibia, although the proximity to the external stimulus is the same. Qualitative comparison of the three-dimensional trabecular bone microstructure images at the two sites paralleled the observed quantitative findings (Fig 5).

DISCUSSION

The data from this 6-month pilot study of end-stage renal disease patients showed some potential of brief daily exposure to low-intensity vibration therapy to alleviate adverse skeletal complications of the disorder. Although intention-to-treat data indicate no benefit of low-intensity mechanical signals as compared to sham control, when only those subjects who retained a high compliance were considered, some salutary outcomes were identified in terms of improving bone quality in the distal tibia of the active group.

Even following post hoc analysis, no benefits of treatment were measured in the distal fibula. The differential treatment response observed at the two skeletal sites equidistant from the source of the external stimulus is likely the result of the tibia's greater participation in weight-bearing, structurally accounting for 90% of the axial force and bending moment consistent with relaxed standing (44). This spatially specific remodeling also suggests that the adaptation is a direct, rather than a secondary response to the mechanical signals, rather than anabolism through factors released systemically. Other skeletal sites beyond the distal tibia were not responsive to low-intensity vibration, whereas hip BMD significantly decreased in the placebo group. It is possible that mechanical signals did not reach the sites such as hip and spine in sufficient amount due to poor transmissibility. Another possibility is that marrow dysfunction results in fewer receptive cells at central sites compared to distal tibia in this population. Future human studies should investigate the response to using different durations and refractory periods to increase the efficacy of low-intensity vibration (45).

Analogous to any pharmacologic treatment, the potential influence of low-intensity vibration critically depends on rigorous adherence to daily usage. In the study reported here, it was only after the four subjects who failed to use the device in any consistent manner were

removed from the analysis that any form of “benefit of treatment” could be identified. These data show that adherence correlated with improvements in several bone measures, including tibia stiffness and parameters characterizing trabecular scale, topology, and connectivity. Reinforcing this conclusion, high adherence in the placebo group revealed no effect on any outcome measures. This dependence on device compliance has been identified in other trials using vibration. A recent pilot study involving 6 months of vibration in patients with Rett syndrome showed an increase in spine BMD when adherence was greater than 65% (46). Further, a study on children with Crohn disease showed only a mild anabolic effect of low-intensity vibration in an intention-to-treat analysis, with increase in QCT-derived BMD while placebo declined. However, post hoc analysis revealed a more potent response in children who used the device with at least 50% adherence, and that every 10% increase in adherence was associated with a 0.06 increase in spine QCT BMD Z-score (19). In a study using low-intensity vibration to build bone in child cancer survivors, it was shown that participants completing 70% of prescribed sessions increased $11.2\% \pm 11.3\%$ in tibial trabecular bone volume as compared to those completing $<70\%$, who decreased $-1.3 \pm 9.9\%$ ($P = .02$) (47). Finally, a study on young women with osteoporosis, but otherwise healthy, showed that once 2 minutes of a 10-minute low-intensity vibration regimen was passed, a benefit to cortical and trabecular bone in the appendicular and axial skeleton, as well as in the paraspinal musculature, was identified (15). In aggregate, these data suggest that a threshold must be passed before any influence of the mechanical signals can be realized.

Our magnetic resonance data showed visible marrow abnormalities in several participants, potentially attributing to the observed only subtle response to mechanical stimulation. However, a proper marrow composition analysis is needed to conclude if bone marrow phenotype is indeed abnormal in patients with end-stage renal disease.

Post hoc analysis showed strong correlations between changes in calf muscle CSA and changes in bone parameters of the distal tibia in the active group. No such significant correlations were observed in the placebo group. Although the causality and underlying mechanism by which low-intensity vibrations affect bone cannot be confirmed by these data, it is evident that participants who showed increased muscle volume had a greater bone response to vibrations. At baseline, calf muscle CSA was significantly correlated with the BMD of the hip ($R = 0.58$, $P = .0017$) and spine ($R = 0.55$, $P = .0034$), suggesting that BMD at central sites in this population are better maintained in individuals with better musculature independent of any intervention. Paralleling these results, a recent study involving postmenopausal women undergoing whole-body vibrations with 60-Hz frequency and 0.6g intensity showed significant improvement in muscle strength after 12 months of 20 min/d, 5 times per week intervention (48). It is likely that the changes we observed in bone were at least partly due to the effect of muscular stimulation on bone, in addition to direct stimulation of bone or mechanical coupling of osteocyte nuclei and the cytoskeleton as previously suggested. In brief, our data highlight the importance of studying the bone-muscle interaction to better understand the underlying mechanism of action of vibration signals.

The vibration device itself recorded all compliance data, and thus provides an accurate and objective measure of adherence. When the electronic record of compliance was compared to

a patient-written log of use, at least in an adult population, there was strong agreement between the two sources (49). However, with several studies now pointing toward the critical role of compliance in efficacy, perhaps greater measures should be taken in clinical trials, as well as in study-independent use of a drug or device, that a patient prescribed with an intervention actually uses the therapy.

Certainly, there is mounting evidence that even in the use of drug-based antiresorptives for the treatment of osteoporosis, compliance is poor, falling off markedly with time (50). To a degree, however, poor compliance and reluctance to continue such therapies may be a result of the public perception of benefits vs consequences of any given therapy (51). That said, there were no serious adverse events reported in this study, or for that matter, any of the subjects completing a range of studies using low-intensity vibration, from children with cerebral palsy (18) to persons of advanced age (21). Nevertheless, it is also important to emphasize that vibration, like any intervention, must be approached with caution. There are large efforts to study the pathologic impact of vibration, such as low back pain, blurred vision, headaches, hearing loss, and white finger disease (24), such that the International Organization for Standardization has released an advisory for Thresholds on Human Exposure to Vibration (52). Even when used in the clinic, some high-intensity vibration devices ($>1g$) are not considered safe to use with subjects who have compromised bone quality (53,54). With the frequency and intensity used in this study, it is considered safe for human exposure for up to 4 h/d.

Participants had abnormally high levels of PTH as a result of the renal disease. Elevated PTH levels are known to adversely affect bone, with deficits arising primarily in the cortical envelope in the form of porosity, which conspires, ultimately, to weaken the bone (55). The association between PTH and cortical bone porosity in renal disease patients was recently confirmed on the basis of high-resolution pQCT imaging at the distal tibia and radius (56). Physical exercise is known to alter PTH secretion while reducing the catabolic effect on bone (57). The data from our study confirm that abnormally high baseline PTH levels are associated with decreased cortical bone density and increased porosity. This correlation was particularly evident in the placebo group, where high PTH continued to jeopardize the quality of the bone. In contrast, subjects in the active group slowed this deterioration, suggesting that these mechanical signals served to mitigate the risk that parallels excessive PTH levels. These results suggest that mechanical stimulation may have a protective effect against the adverse effects of excess PTH on cortical bone in this population.

Several recent studies have investigated the effect of mechanical stimulation in healthy human subjects. Twelve months of whole-body vibration therapy showed no significant effect on bone outcomes in healthy postmenopausal women assessed by high-resolution pQCT and DXA compared to no vibration therapy (58). Another study involving healthy men and women ranging in age from 65 to 102 years did not show any significant benefit of daily 10 minutes of vibration therapy after 24 months intervention compared to placebo on the basis of QCT-derived volumetric BMD at the hip and spine (21). Low-intensity vibration is a surrogate for exercise, and it is not clear if young, healthy adults with good bone would benefit from this intervention because they are already seeing the mechanical signals during normal ambulation/activity. On the other hand, low-intensity vibration may be ideally suited

for individuals who have a limited capacity to exercise, for example, end-stage renal disease patients and children with cerebral palsy. Although mechanosensitive cells might be present in these populations, external signals might be needed for activating these cells, unlike in young, active adults. Furthermore, it is not clear what the refractory period would be for the cellular response to mechanical stimuli.

We note several differences between these previous reports on the effect of mechanical stimulation in human subjects compared to our study, including study population, measurement modality, and primary outcome measure. For example, the most significant effect of the intervention in our study involved parameters related to microstructural connectivity —tibia stiffness and trabecular plate-to-rod ratio — which were not assessed in previous studies, except in Dudley-Javoroski et al. (59). Furthermore, differences in DXA measures over the 6-month intervention were not discernable at spine or hip in our study. It is possible that careful three-dimensional microstructural matching and advanced analysis is needed to detect subtle localized changes induced by low-intensity mechanical stimulation.

Finite-element analysis in the active group with high adherence to device usage showed significant improvement in tibia whole cross-section stiffness, which depends on the strength of both cortical and trabecular compartments. Increase in stiffness can be attributed to the improvement in the trabecular bone characterized by parameters describing scale (trabecular BMD, Tb.N, and Tb.S) and topology (plate-to-rod ratio). On the other hand, cortical bone parameters (cortical BMD and porosity) did not show any statistically significant change as a result of exposure to mechanical stimulation, suggesting increase in whole-section tibia stiffness is due to improvement in trabecular but not cortical bone.

The present study has several limitations. First, the sample size was small and heterogeneous with respect to the cause of renal failure, duration after diagnosis, body habitus, and PTH levels. Nevertheless, all participants on maintenance dialysis were stable and had no significant comorbidities. Overall, vitamin D therapy did not change and only minor modifications were made in the phosphate binder regimen during the study period. Second, although MRI-based finite-element analysis is sensitive to the combined alterations in bone's microstructure and volume, it does not capture changes that can occur in tissue properties, for example, resulting from changes in local mineralization. Similarly, the MRI voxel size was on the order of trabecular thickness; however, prior studies have shown that MRI-based analysis can detect subtle changes in cortical and trabecular microstructure resulting from disease or therapeutic intervention (33,60,61). Furthermore, despite the placebo device emitting an audible tone, the lack of vibration may have been noticeable. However, the adherence in the placebo and active groups were not significantly different, suggesting that participants in the placebo group were unaware of the type of device assigned to them (Fig 4). Lastly, several participants had particularly poor adherence. To improve compliance in future studies, continual monitoring of device adherence throughout the study and feedback to patients would be necessary. Longer-term studies would help discriminate effects. Our study used only one set of vibration parameters. Incorporating a refractory period, using the device longer, or changing intensity or frequency would provide insight into a path to improve efficacy of the intervention.

Overall, the intervention was well tolerated, and no adverse effects associated with device use were reported. Outcomes and adherence thresholds identified from this pilot study could guide future longitudinal studies involving vibration therapy, in terms of statistical power needed to detect intergroup treatment effects. Lastly, larger clinical trials, run for longer periods, are needed to determine if vibration therapy as a nondrug intervention is effective for mitigating fracture risk, without complicating the already excessive medications these patients inevitably must tolerate.

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Figure 1. Illustration of low-intensity vibrational intervention in which a low-intensity acceleration is delivered in a vertical direction, requiring approximately a 90 μ displacement of the top platen.

Figure 2. Examples of axial magnetic resonance images of the distal tibia and fibula metaphysis; delineation of periosteal boundaries; and three-dimensional rendition after disconnection of soft tissue.

Figure 3.

Transverse magnetic resonance images through the distal tibia in three patients obtained at baseline showing (a) relatively normal bone, (b) severely disconnected trabecular network, and (c) presence of marrow fibrosis, which could be a result of high-dose corticosteroid use.

Figure 4.

Distribution of adherence for participants assigned to the active mechanical stimulation ($N=14$) and placebo groups ($N=15$). Adherence was not significantly different between the two groups ($P=.59$).

Figure 5. Comparison of volume rendered distal tibia and fibula microstructure reconstructed from high-resolution magnetic resonance images at baseline and after 6 months in a participant of the active mechanical stimulation group. The magnified trabecular bone subvolumes selected through a qualitative examination of individual trabecular elements for illustrative purposes suggest bone accrual in the distal tibia but not in the distal fibula.

TABLE 1

Characteristics of Participants Randomized to Active or Placebo Device Use

	Active N = 14	Placebo N = 15
Mean Age (SD), yr	50 (11)	48 (10)
Sex, <i>n</i> (%)		
Male	8 (57)	9 (60)
Female	6 (43)	6 (40)
Mean body mass (SD), kg	72.7 (18.7)	69.7 (16.4)
Mean height (SD), m	1.69 (0.092)	1.68 (0.070)
Mean body-mass index (SD), kg/m ²	25.3 (5.33)	24.4 (4.36)
Cause of renal disease, <i>n</i> (%)		
Hypertension	6 (43)	6 (40)
Diabetes	1 (7)	1 (7)
Focal segmental glomerulosclerosis	4 (29)	2 (13)
Other	3 (21)	6 (40)
Median dialysis duration [range], yr	2.13 [0.172–15.2]	3.52 [0.339–7.12]
Median intentional exercise [range], min/day	25 [0–100]	39 [0–90]
Medication intake, <i>n</i>		
Prednisone	2	2
Cinacalcet	7	3
Vitamin D sterol	15	13
Phosphate binder	14	14

SD, standard deviation.

None of the parameters were significantly different between the two groups.

TABLE 2

Percent Changes Between the Two Time Points for the Outcomes (Reported as Mean $\pm$ SD), Based on the Intention-to-Treat Data Analysis

	Active % Change	Placebo % Change	<i>P</i>
Tibia stiffness, GPa	2.43 $\pm$ 5.15	1.61 $\pm$ 6.90	.72
Tibia trabecular BV/TV, %	0.30 $\pm$ 3.82	-1.21 $\pm$ 5.77	.42
Tibia trabecular thickness, mm	-0.02 $\pm$ 1.32	0.29 $\pm$ 1.83	.70
Tibia trabecular number	0.30 $\pm$ 2.85	-1.53 $\pm$ 4.85	.23
Tibia trabecular separation, mm	-0.24 $\pm$ 3.31	1.97 $\pm$ 5.59	.22
Tibia trabecular plate-to-rod ratio	3.59 $\pm$ 8.59	1.26 $\pm$ 10.2	.52
Tibia trabecular BMD, mg/cm ³	0.95 $\pm$ 2.68	-0.68 $\pm$ 3.64	.21
Tibia cortical porosity, %	2.26 $\pm$ 13.0	1.63 $\pm$ 11.8	.89
Tibia cortical BMD, mg/cm ³	-0.26 $\pm$ 1.25	-0.04 $\pm$ 0.57	.58
Hip BMD, mg/cm ²	-1.27 $\pm$ 3.48	-1.17 $\pm$ 2.48	.93
Lumbar PA spine BMD, mg/cm ²	-1.09 $\pm$ 2.25	-1.34 $\pm$ 4.21	.85
Calf muscle CSA, cm ²	-1.72 $\pm$ 3.47	-0.40 $\pm$ 6.72	.58
PTH, pg/mL	51.0 $\pm$ 134	104 $\pm$ 340	.60

BMD, bone mineral density; BV/TV, bone volume/total volume; CSA, cross-sectional area; PA, posteroanterior; PTH, parathyroid hormone; SD, standard deviation.

The *P* value indicates the significance of the difference in percent change in parameters between the active and placebo groups.

TABLE 3

Baseline, 6-Month Absolute Values, and Percent Changes Between the Two Time Points for the Outcomes (Reported as Mean $\pm$ SD), Based on the Post Hoc Longitudinal Data Analysis

	Baseline	6 Months	% Change	P
Tibia stiffness, GPa				
Active	1.11 $\pm$ 0.09	1.17 $\pm$ 0.11	5.26 $\pm$ 4.5	.022 *
Placebo	1.20 $\pm$ 0.17	1.21 $\pm$ 0.18	0.94 $\pm$ 6.1	.49
Tibia trabecular BV/TV, %				
Active	8.98 $\pm$ 0.06	9.15 $\pm$ 0.60	1.87 $\pm$ 2.3	.078
Placebo	9.69 $\pm$ 1.53	9.56 $\pm$ 1.56	-1.23 $\pm$ 5.3	.30
Tibia trabecular thickness, mm				
Active	0.104 $\pm$ 0.004	0.104 $\pm$ 0.004	0.16 $\pm$ 1.2	.75
Placebo	0.108 $\pm$ 0.014	0.109 $\pm$ 0.012	0.12 $\pm$ 1.7	.73
Tibia trabecular number				
Active	0.862 $\pm$ 0.04	0.877 $\pm$ 0.05	1.70 $\pm$ 1.40	.018 *
Placebo	0.893 $\pm$ 0.095	0.880 $\pm$ 0.096	-1.39 $\pm$ 4.32	.16
Tibia trabecular separation, mm				
Active	1.06 $\pm$ 0.05	1.04 $\pm$ 0.06	-1.84 $\pm$ 1.55	.020 *
Placebo	1.03 $\pm$ 0.13	1.04 $\pm$ 0.14	1.76 $\pm$ 5.00	.12
Tibia trabecular plate-to-rod ratio				
Active	1.33 $\pm$ 0.27	1.36 $\pm$ 0.28	6.51 $\pm$ 3.8	.004 *
Placebo	1.27 $\pm$ 0.30	1.31 $\pm$ 0.31	1.06 $\pm$ 10	.64
Tibia trabecular BMD, mg/cm ³				
Active	202 $\pm$ 32	207 $\pm$ 30	2.34 $\pm$ 2.3	.034 *
Placebo	216 $\pm$ 58	217 $\pm$ 49	-0.76 $\pm$ 3.3	.31
Tibia cortical porosity, %				
Active	39.5 $\pm$ 7.0	39.5 $\pm$ 5.6	-1.64 $\pm$ 11	.71
Placebo	37.9 $\pm$ 8.3	38.5 $\pm$ 6.3	3.07 $\pm$ 13	.27
Tibia cortical BMD, mg/cm ³				
Active	1135 $\pm$ 46.2	1137 $\pm$ 43	0.13 $\pm$ 0.42	.45
Placebo	1159 $\pm$ 45.3	1150 $\pm$ 50	-0.25 $\pm$ 1.08	.33
Hip BMD, mg/cm ²				
Active	1.00 $\pm$ 0.19	1.00 $\pm$ 0.19	0.14 $\pm$ 4.1	.93
Placebo	0.98 $\pm$ 0.20	0.91 $\pm$ 0.20	-1.65 $\pm$ 2.7	.0049 *
Lumbar PA Spine BMD, mg/cm ²				
Active	1.06 $\pm$ 0.11	1.05 $\pm$ 0.11	-0.92 $\pm$ 2.3	.32
Placebo	1.05 $\pm$ 0.22	1.03 $\pm$ 0.23	-1.32 $\pm$ 3.7	.11
Calf muscle CSA, cm ²				
Active	67.4 $\pm$ 13.0	67.1 $\pm$ 12.3	-0.34 $\pm$ 2.4	.77
Placebo	60.0 $\pm$ 13.9	60.2 $\pm$ 14.0	-1.08 $\pm$ 6.2	.44
PTH, pg/mL				

	Baseline	6 Months	% Change	P
Active	333 ± 222	399 ± 238	34 ± 69	.24
Placebo	373 ± 316	352 ± 306	94 ± 299	.18

BMD, bone mineral density; BV/TV, bone volume/total volume; CSA, cross-sectional area; PA, posteroanterior; PTH, parathyroid hormone; SD, standard deviation.

Participants who complied more than the median adherence (70%) in the active mechanical stimulation arm were considered “active” and all other participants are grouped as “placebo.” The *P* value indicates the significance of the percent change in parameters between the two time points within each group.

* Indicates statistically significant changes.

TABLE 4

Correlation Between the 6-Month Changes in Measured Parameters and Daily Device Adherence in the Active Group Using Post Hoc Analysis

	Change (%) vs Adherence	
	R	P
Tibia stiffness	0.66	.050 *
Tibia trabecular BV/TV	0.87	.0021 *
Tibia trabecular thickness	0.80	.0095 *
Tibia trabecular number	0.75	.021 *
Tibia trabecular separation	−0.77	.016 *
Tibia trabecular plate-to-rod ratio	0.75	.020 *
Tibia trabecular BMD	0.60	.11
Tibia cortical porosity	−0.86	.0028 *
Tibia cortical density	−0.15	.72
Hip BMD	0.14	.72
Lumbar spine BMD	−0.29	.44
Calf muscle CSA	0.70	.12
PTH	0.41	.28

BMD, bone mineral density; BV/TV, bone volume/total volume; CSA, cross-sectional area; PTH, parathyroid hormone.

* Indicates statistically significant changes.

TABLE 5

Correlation Between the 6-Month Changes in Measured Parameters and Changes in Calf Muscle CSA in the Active Group Using the Post Hoc Analysis

Change (%) vs Change (%) in Calf Muscle CSA		
	R	P
Tibia stiffness	0.85	.033 *
Tibia trabecular BV/TV	0.91	.011 *
Tibia trabecular thickness	0.38	.46
Tibia trabecular number	0.92	.0082 *
Tibia trabecular separation	−0.94	.0057 *
Tibia trabecular plate-to-rod ratio	0.70	.12
Tibia trabecular BMD	0.44	.38
Tibia cortical porosity	−0.44	.38
Tibia cortical density	0.29	.57
Hip BMD	0.26	.62
Lumbar spine BMD	0.19	.72
PTH	0.31	.55

BMD, bone mineral density; BV/TV, bone volume/total volume; CSA, cross-sectional area; PTH, parathyroid hormone.

* Indicates statistically significant changes.