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Research Article

Bone Remodeling Assessment in Patients with Renal Osteodystrophy Undergoing Vibrational Therapy: A MRI Finite Element Analysis Approach

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ABSTRACT

Introduction: Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is a bone remodeling disorder resulting from impaired renal function. Patients with CKD have an increased risk of fractures, and current treatments offer limited effectiveness. Alternative interventions have been proven to be effective such as Low-Intensity Vibrational therapy (LIV) that triggers an anabolic bone response increasing the Bone Mineral Density (BMD) with no adverse effects. Our study aims to use MRI based finite element modeling to simulate bone strains in patients with Renal Osteo Dystrophy (ROD) at baseline and determine whether the results can help identify the relationship between the simulated strains and actual bone remodeling after Low-Intensity Vibration (LIV) therapy. By establishing this relationship, our study seeks to provide insight into the microarchitectural changes in bone that occur in response to LIV therapy, which could potentially lead to improved treatment strategies for ROD patients.

Materials and methods: The study utilized retrospective data from a randomized controlled trial, which assigned 30 patients with ROD equally to active and placebo groups and received daily 20 minutes treatment with LIV for 6 months. MRI scans of the patients' distal tibias were conducted at baseline, and 6 months follow-up, and the resulting strain was calculated using Finite Element Analysis (FEA). The study also utilized baseline patient data to develop a multiple linear regression model to analyze the change in Bone Volume Fraction (BVF) over time.

Results: We found a positive correlation between baseline trabecular strain and percent change in trabecular BVF at 6 months follow-up ($r=0.62$, $P=0.045$) and between baseline trabecular strain and percent change in BVF in the center of the trabecular region ($r=0.65$, $P=0.03$). However, among placebo device users, there was a negative correlation between these variables in the right trabecular region ($r=-0.76$, $P=0.02$). Additionally, high-strain voxels experienced a greater percent change in BVF than low-strain voxels ($P<0.0001$).

Conclusion: This study discovered a link between initial trabecular strain and the efficacy of LIV therapy in patients diagnosed with ROD, suggesting that elevated baseline strain levels correspond with substantial alterations in BVF due to LIV. The study underlined the need to measure baseline trabecular strain instead of relying solely on initial BVF, demonstrating its pivotal role in treatment success. Further investigations into the relationship between these bone parameters would contribute to a better understanding and optimization of therapeutic approaches.

Keywords: MRI; Trabecular strain; Chronic kidney disease; Low-Intensity Vibration (LIV); Bone Mineral Density (BMD)

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INTRODUCTION

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is a metabolic bone disorder that results from an impairment of the renal parenchyma, reducing its ability to convert vitamin D to its active form [1]. It is characterized by secondary hyperparathyroidism, which becomes more prevalent as kidney function declines. Although increased PTH secretion can initially help increase calcium and vitamin D and decrease phosphate levels, prolonged hyperparathyroidism can be maladaptive [2]. Consequently, this initiates a series of events that can negatively derange the morphology and microarchitecture of bone, causing Renal Osteodystrophy (ROD) [3].

Patients with CKD have more than 2.5 times higher risk of fractures than those without CKD. Recent studies have suggested that men and women on maintenance dialysis have an incidence rate of hip fracture of 7.5 and 13.6 per 1,000 person years, respectively, compared to the rates of 5.0 and 7.5 per 1,000 person years in men and women in the general population [4]. As the general population experiences increased financial burdens and mortality rates due to fractures, these rates are considerably higher for patients with multiple comorbidities such as CKD [5-7].

The present approach for treating ROD has been aimed at controlling the high bone turnover through the use of active vitamin D and/or calcimimetics, as well as simultaneously preventing adynamic bone disease by avoiding excessive use of these agents. However, there is little evidence to indicate that this strategy has effectively improved skeletal outcomes in ROD patients. Additionally, patients with CKD have decreased glomerular filtration rates, further complicating the effectiveness of pharmaceutical treatments such as bisphosphonates [8-9]. Luckily, other interventions are available, including surgical procedures and Low Intensity Vibration (LIV), with varying effectiveness based on patient population and individual characteristics. LIV is a promising technique used to enhance the structural integrity of bones. It is a relatively recent therapy in which patients stand on a platform that emits high frequency low intensity vibrations [10-13]. Studies have revealed that this method triggers an anabolic response in bone, resulting in different degrees of increased Bone Mineral Density (BMD) in various patient disease states and experimental conditions [14-16]. BMD measurements alone are insufficient to fully capture the significant micro architectural or regional modifications in response to LIV. Furthermore, on the cellular level, the downstream effects of the vibrations on osteocytes have not been fully understood in humans but have shown promising results in animal models [17]. Hence, further research elucidating the mechanisms of LIV in clinical cohorts and relevant subpopulations is warranted.

According to Wolff's law, bone microarchitecture will adapt to the mechanical forces imposed upon it [18]. For example, it is expected that localized regions of the tibia which experience higher mechanical strain will show an increase in Bone Volume Fraction (BVF) relative to non-weight-bearing, stabilizing areas of bone in the fibula. Previous research has demonstrated that increased strain caused by dynamic loading leads to changes in enzymatic activity and an increase in bone formation [19]. Exercise induced loading has also been shown to increase bone mass and decrease bone resorption [20,21]. The production of secondary messengers in bone cells in response to mechanical stretching and extracellular fluid flow, which are associated with bone strain, promotes the formation of new bone [22-24].

Currently, the only methods of evaluating volumetric bone strain *in vivo* include the use of imaging-based finite element analysis [25]. MRI has been shown to be sensitive in detecting subtle changes to trabecular bone that impacts the measured strain of bone and is considered a safe alternative to computed tomography scans since it does not involve the use of ionizing radiation. Previous studies have suggested that applying LIV on bone regions may lead to decreases in resorption and increases in measured BMD through local strain. Performing MRI based finite element analysis modeling to simulate similar strains in patients with ROD at baseline can aid in identifying the specific sites of bone remodeling that may later result from LIV therapy. The purpose of this exploratory study is to elucidate whether *in vivo* bone strain localizes with bone remodeling (defined by BVF) in response to vibrational therapy using simulated strain as a surrogate of micro architectural changes in bone.

MATERIALS AND METHODS

Patients

This retrospective study used data from a previously reported cohort of thirty participants with ROD who were randomly assigned to either an active LIV device group (n=15) or a placebo group (n=15) for 20 minutes daily over a period of six months. This population sample comprises patients with renal osteodystrophy, a condition characterized by bone disorders due to alterations in mineral metabolism and bone remodeling resulting from chronic kidney disease. Informed consent was obtained from all study participants. Participants were excluded based on low device adherence, pregnancy, recent injury due to a fall within six months, significant comorbidities, anticipated transplantation, amputation of lower extremities, inability to climb two flights of stairs or walk three blocks, and any previous bone fracture within six months. The institutional review board of the university approved this study.

Randomization

In the original parent study, participants were randomly assigned to either an active or placebo. Both groups were given a LIV treatment device to use at home. The devices for both groups looked the same and emitted a tone at 500 Hz to conceal the group assignment. The randomization was done by a research coordinator who was not involved in analyzing the study outcomes. All other investigators were blinded to the group assignment to avoid bias.

Intervention

The active group was provided with LIV devices that contained an active actuator designed to oscillate vertically at 30 Hz and

0.3 g, regardless of body weight. The placebo group was provided with identical devices that lacked an active actuator. Participants were instructed to stand on the devices for 20 minutes each day over the 6 months study duration, with knees neither locked nor bent and in bare feet or with stockings. The devices collected information on data, time, and duration of use to determine patients' compliance with treatment.

Magnetic Resonance Imaging (MRI)

MRIs were conducted on patients at baseline and completion of the 6-month study using a 1.5 Tesla whole body MRI scanner (Siemens Sonata, Erlangen, Germany) with a fast large angle spin echo pulse sequence (flip angle 140°, TR/TE 80 ms/11.8 ms, 16.67 kHz bandwidth, 137 × 137 × 410 μm^3 voxel size in 15 minutes) to image the distal tibia metaphysis (3% site).

Finite element analysis

Image segmentation was conducted using a custom-designed operator guided software and algorithm. A local thresholding algorithm was used to reduce the effect of MRI receiver coil sensitivity variations. BVF maps were created by linearly scaling MRI pixel intensity values from 0 to 100, corresponding to pure marrow and pure bone, respectively. The resulting images served as input for the micro level finite element model, and simulated compression was applied to the whole section tibia model along the bone's axial direction as previously described, resulting in a strain map for the entire analysis volume.

Regional BVF and strain analysis

Trabecular BVF was calculated as the average voxel Bone Volume/Total Volume (BV/TV) in five 3D Regions Of Interest (ROIs) anterior, posterior, medial, lateral, and center that equally represented the different areas of the cross-sectional images. For each ROI, the average bone strain was calculated using the strain maps generated as described above.

Voxel wise BVF and strain analysis

To assess the effect of voxel wise strain on change in BVF, strain values were obtained using whole section tibia models constructed from baseline MRI scans of the 20 patients included in the study and simulating axial compression by FEA. Voxels within each model were stratified as "high" or "low" strain based on a uniform threshold strain level of 1.0. The percent change in BVF at follow up was computed for all voxels measured.

Statistical analysis

We used JMP Discovery Software, Version 12.0 (SAS institute, Inc., Cary, NC) for statistical analyses. We assumed values of $P<0.05$ to indicate statistical significance. Pearson correlation coefficients were used to evaluate normally distributed data, and we established a multiple linear regression for the percent change in BVF of trabecular bone from baseline characteristics. The association between baseline voxel strain and percent change in BVF was analyzed by one-way t-tests. Differences in device adherence between active and placebo groups were determined using as determined by Welch two sample t-test.

RESULTS

Participant characteristics

After excluding patients with device adherence under 15% (two active, three placebo), a total of 25 participants remained. One active group patient withdrew due to an unrelated broken leg, and two placebo group patients had abnormalities in their marrow, cortical, and trabecular regions. Additionally, two MRI scans (one active, one placebo) produced unusable images. This resulted in a final sample of 20 participants who were included in the analyses. The active group had a mean percent adherence of 70.2 ± 26.2, while the placebo group had a mean percent adherence of 82.4 ± 13.3. The difference in adherence between the two groups was not statistically significant, according to the Welch two sample t-test ($P=0.21$). Table 1 represents the patients' characteristics.

Table 1: Patient characteristics.

	Active n=11		Placebo n=9	
Age, yr	**47**	**(10)**	**49**	**(10)**
Gender*, No. (%)				
Female	5	(45)	4	(44)
Male	6	(55)	5	(56)
Weight, kg	67.9	(16.8)	65.8	(14.9)
Height, m	1.68	(0.095)	1.66	(0.085)
Body mass index, kg/m^2	23.7	(3.63)	23.5	(3.54)

Dialysis duration, median (range), months	25.3	(2.1-153.2)	42.9	(4.1-86.1)
Parathyroid hormone, median (range), pg/mL	312	(176-1022)	356	(208-886)
Baseline alkaline phosphatase, median (range), U/L	42.37	(14.19-89.56)	30.59	(19.66-62.84)

Note: Values are expressed as mean (SD) unless otherwise indicated.

*Due to rounding, percentages may not total 100.

Association between MRI derived average baseline strain and change in BVF among study groups

Among participants in the active group, there was a positive correlation between average baseline trabecular strain and average percent change in trabecular BVF at 6 months follow-up (r=0.62, P=0.045). However, this correlation was not observed in the placebo group (r=0.44, P=0.24) (Figure 1).

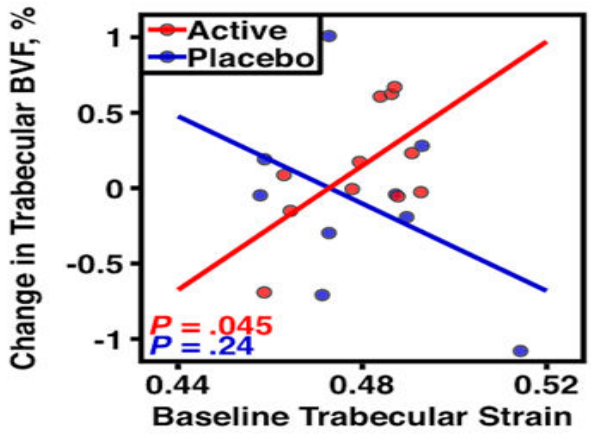

Figure 1: Average baseline trabecular strain and average percent change in trabecular Bone Volume Fraction (BVF). Data shown is among active (n=11) and placebo (n=9) patients. Averages were computed from the entire trabecular region.

Association between MRI derived regional baseline strain and change in BVF among study groups

When examining individual regions, among active device users, there was a positive correlation between baseline trabecular strain and percent change in BVF in the center of the trabecular region (r=0.65, P=0.03). However, among placebo device users, there was a negative correlation between these variables in the right trabecular region (r=-0.76, P=0.02) (Table 2). The strengths of these relationships are represented spatially in Figure 2. An example strain map of trabecular bone is shown in Figure 3.

Table 2: Correlations between baseline trabecular strain and change in trabecular BVF by region.

	Active n=11		Placebo n=9	
Region	**r**	**P**	**r**	**P**
Center	0.65	0.03*	-0.4	0.28
Left	0.44	0.18	0.11	0.79
Anterior	0.51	0.11	-0.25	0.51
Right	-0.16	0.63	-0.76	0.02*
Posterior	0.18	0.59	-0.07	0.86
Total[a]	0.61		-0.44	0.24

Note: BVF: Bone Volume Fraction.

*Denotes significance.

[a]Average correlation for the entire trabecular region.

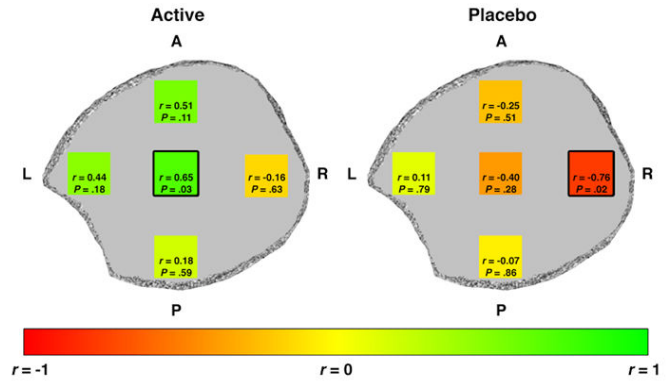

Figure 2: Strength of relationships between baseline trabecular strain and percent change in trabecular bone volume fraction. Strain was mapped by region onto a representative left femur, among (left) active (n=11) and (right) placebo (n=9) participants. Regions outlined in black are significant at P<0.05.

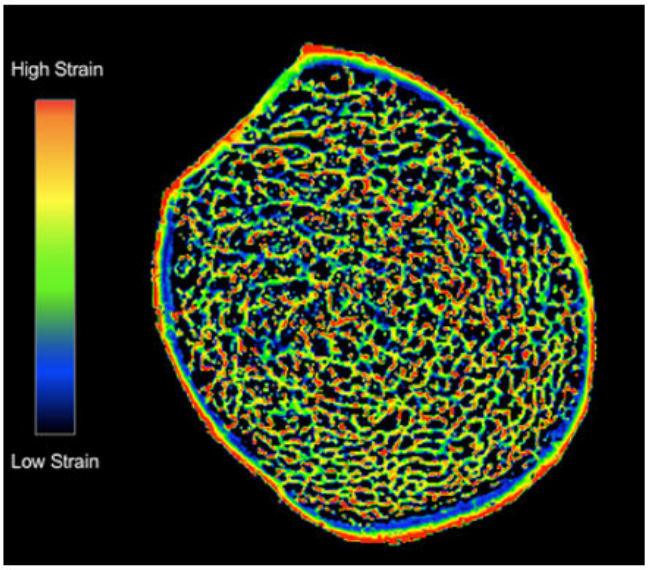

Figure 3: Cross-sectional strain map of trabecular bone. An example strain map is shown, identifying high and low strain regions.

Association between voxel-wise baseline strain and change in BVF

Voxel wise values of baseline strain and percent change in BVF at follow-up were collected and analyzed for association. Scans contained a mean voxel count of 997,568 (SD=218,746.7). After stratifying voxels by baseline strain into low and high strain groups, scans had an average composition of 14.02% high strain and 85.98% low strain (SD=2.54%) voxels. The percent change in BVF was found to be greater in high-strain groups compared to low strain groups (P<0.0001 for all 11 active cases and 7 of 8 placebo cases *via* one-way t-tests) (Figure 4).

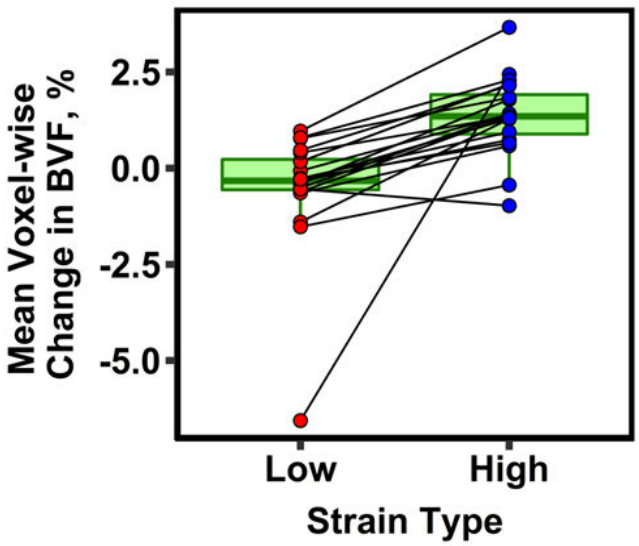

Figure 4: Mean voxel wise percent change in BVF of low and high strain voxels. Connected points represent individual patient scans (n=20) with averages computed across all voxels of a given strain classification.

DISCUSSION

In this study, we found that baseline trabecular strain was positively correlated with the percent change in BVF in the central region for the active group patients and negatively correlated with the percent change in BVF in the lateral region for placebo participants. This suggests that LIV treatment affects various regions of bone differently, and higher levels of strain are related to greater changes in BVF due to the transmission of LIV. Strain is known to increase the flow of interstitial fluid in the canaliculi of bone, which can lead to the activation of mechanosensitive cells such as osteocytes. Osteocytes transport signaling molecules involved in bone metabolism in response to activation by mechanical strain. Strain was used as a surrogate for identifying regions that transmit LIV signals since simulating LIV itself would require a more complicated and dynamic system.

An association between baseline trabecular strain and change in trabecular BVF was identified in active group participants, suggesting the efficacy of LIV treatment is proportional to baseline strain. For patients with lower baseline strain, this relationship resulted in a decrease in BVF. One interpretation of this result is that a floor effect exists between these variables such that in patients with baseline strain below a certain threshold, LIV do not sufficiently increase the fluid flow in the canaliculi and activate osteocyte signaling.

Regions of higher strain obtained from finite element analysis coincide with regions that transmit mechanical signals from the device to the upper skeleton since strain is calculated by applying a force to the top and bottom of the tibia, similar to LIV transmission while standing. Through visual inspection of cross-sectioned bone strain, localized variation in strain can be observed within the microarchitecture across the trabecular surface (Figure 3). Thus, examining changes in bone structure on a regional level may still fail to detect highly localized changes in bone. In a voxel-wise analysis of bone strain, individual voxels of patient scans were stratified into groups of low and high baseline strain and compared to change in BVF. High strain voxels were strongly associated with increases in BVF for 19 of 20 cases tested, demonstrating that quantifiable differences in BVF emerge depending on the classification of baseline strain voxels.

The baseline BVF was compared to the change in BVF over time and showed no correlation, showing the inadequacy of baseline BVF in delineating treatment outcomes. Measurement of baseline trabecular strain was necessary to estimate the changes in BVF.

The methods we used to assess BVF and strain distribution may be extended to other osteoporosis treatments and metabolic bone diseases. For instance, diffusion MRI scans have been used as a predictive biomarker in oncology to measure water mobility in tissue. An apparent diffusion coefficient can be calculated from diffusion MRI scans and modeled as a predictor for the effectiveness of various radiation therapy treatment options, similar to how strain was utilized to estimate the effectiveness of LIV treatment in this study.

Previous research has shown that bone turnover markers within 6 months of starting a new treatment have been predictive of the overall change in BMD in subsequent years with continued treatment. However, baseline bone turnover markers have been found not to be predictive of BMD response to therapy, suggesting that a lag time may be necessary for changes to be detected in BMD. A potential reason for this is the one dimensional nature of BMD measurements. Localized changes in bone metabolism may occur in relation to baseline measurements, which can only be detected by the use of more precise methods for detecting subtle changes in metabolic activity, such as by measuring regional bone strain, as demonstrated in this study.

This study had several limitations. First, the sample size was limited due to excluding patients with low device adherence or abnormalities. Second, the measurements of baseline trabecular strain were limited to distinct regions and excluded other portions of bone. Third, the placebo treatment for LIV emitted only a sound and not vibrations, which may have been detectable by patients. This was partially accounted for by excluding patients with low device adherence.

CONCLUSION

In conclusion, this pilot study demonstrated a correlation between baseline trabecular strain and the effectiveness of LIV therapy in patients with ROD. The findings indicate that LIV affects different bone regions distinctly, with higher baseline strain levels associated with more significant changes in BVF resulting from LIV transmission. Moreover, the study emphasized the insufficiency of baseline BVF as an estimator of treatment outcomes, highlighting the necessity of measuring baseline trabecular strain. By further exploring and confirming the relationship between bone parameters like BVF and bone strain, we could enhance clinicians' capabilities to monitor therapy effectiveness, facilitating the design of individualized treatment strategies. This approach will ultimately lead to optimized patient outcomes in managing ROD.

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