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The Effects of High-dose Calcitriol and Individualized Exercise on Bone Metabolism in Breast Cancer Survivors on Hormonal Therapy: A Phase II Feasibility Trial

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Abstract

Introduction—Cancer-treatment-induced bone loss (CTIBL) is a long-term side effect of breast cancer therapy. Both calcitriol and weight-bearing exercise improve bone metabolism for

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Trial was retrospectively registered.

osteoporotic patients, but are unproven in a breast cancer population. We used a novel high-dose calcitriol regimen with an individualized exercise intervention to improve bone metabolism in breast cancer survivors.

Methods—We accrued 41 subjects to this open label, 2×2 factorial, randomized feasibility trial. Breast cancer survivors were randomized to receive: 1) calcitriol (45 micrograms/week), 2) individualized exercise with progressive walking and resistance training, 3) both, or 4) a daily multivitamin (control condition) for 12 weeks. Primary outcomes included changes in biomarkers of bone formation, bone resorption, and the bone remodeling index, a composite measure of bone formation and resorption. Safety measures included clinical and biochemical adverse events. A main effects analysis was used for these endpoints.

Results—Hypercalcemia was limited to 3 Grade I cases with no Grade 2 cases. Among exercisers, 100% engaged in the prescribed aerobic training and 44.4% engaged in the prescribed resistance training. Calcitriol significantly improved bone formation (Cohen's $d=0.64$; $p<0.01$), resulting in a non-significant increase in the bone remodeling index (Cohen's $d=0.21$; $p=31$). Exercise failed to improve any of the bone biomarkers.

Conclusions—Both calcitriol and exercise were shown to be feasible and well tolerated. Calcitriol significantly improved bone formation, resulting in a net increase of bone metabolism. Compliance with the exercise intervention was sub-optimal, which may have led to a lack of effect of exercise on bone metabolism.

Keywords

Calcitriol; Exercise; Breast Cancer; Hormonal Therapy; Bone Metabolism; Bone Health

Introduction

Cancer-treatment-induced bone loss (CTIBL) is a long-term side effect of breast cancer therapy; up to 80% of breast cancer survivors have osteoporosis or osteopenia [12, 28, 38], which is a reduction in bone mineral density that increases the risk of fracture. The primary cause of CTIBL in breast cancer survivors is hypogonadism, which can result from hormone therapy or chemotherapy (by inducing early menopause) [21]. These treatments result in a precipitous drop in endogenous estrogen levels, often resulting in rapid bone loss. The hormonal therapies that contribute significantly to CTIBL are aromatase inhibitors (AI) for postmenopausal survivors and tamoxifen for premenopausal survivors [29]. Postmenopausal women without breast cancer lose an average of 1% of their bone mineral density (BMD) annually, while postmenopausal breast cancer survivors on AI lose between 2–8% of their BMD, and premenopausal survivors lose approximately 2% of their BMD annually [14, 15, 24, 41]. These losses translate into an increased fracture risk, 2–5 times greater in breast cancer survivors than in those without cancer [11, 26].

Bisphosphonates (and more recently RANKL inhibitors), the standard of care for osteoporosis therapy, significantly reduce bone loss and fracture risk. However, bisphosphonate use, especially long-term use, has been associated with osteonecrosis of the jaw and atypical femoral fractures. Although the absolute risk of developing osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) while using bisphosphonates is

relatively low, the Federal Drug Administration has issued a labeling change reflecting these risks and has suggested reevaluating the need for continued bisphosphonate therapy beyond 3–5 years on an individual basis. Clearly, there is a need for additional therapies for osteoporosis in individuals who cannot take or who had to discontinue bisphosphonate therapy.

Calcitriol, the metabolically active form of vitamin D, is effective in the prevention of bone loss and fractures [3, 31]. However, traditional calcitriol therapy, usually administered once or twice daily, is limited by the development of hypercalcemia and hypercalcuria, which is an elevation of calcium in the blood and urine, respectively. Employing intermittent dosing of calcitriol allows for substantial dose escalation while significantly reducing hypercalcemia and hypercalcuria rates [7].

Exercise, specifically weight-bearing exercise and resistance training, improves bone metabolism [1, 4, 33] and increases BMD [20, 22, 39]. The vast majority of studies that examined the effect of exercise on bone health used populations of participants with osteoporosis/osteopenia, with very little research on the effect of exercise on bone health in a cancer-specific population. We modified an existing individualized, home-based exercise intervention (Exercise for Cancer Patients [EXCAP[®]]), originally designed specifically for cancer patients and survivors, to best improve bone metabolism. Previous EXCAP interventions have been used to improve cancer-related fatigue and insomnia in cancer patients [25, 27, 30].

In this study we attempted to determine the feasibility and tolerability of a weekly, high-dose calcitriol regimen and to establish the effect of this calcitriol regimen and an individualized exercise intervention on bone metabolism biomarkers in breast cancer survivors receiving hormonal therapy. For this pilot study, we used bone metabolism biomarkers as our main efficacy outcome in lieu of BMD because biomarkers respond more quickly to therapy, are non-invasive, and predict future outcomes, such as fractures [23, 40, 43].

Methods

Enrollment

Forty-one eligible participants were enrolled at the University of Rochester Medical Center (URMC) between April and September 2009. This study was reviewed and approved by the URMC Research Subjects Review Board (RSRB). All research participants gave written informed consent. An independent safety monitoring committee periodically reviewed the safety data.

Eligible subjects were females diagnosed with breast cancer (stage 0–III) within the previous five years. Breast cancers were hormone receptor-positive, and patients were actively receiving hormone therapy. A five year window after diagnosis was chosen because this is the period in which breast cancer patients would receive hormone therapy and be at greatest risk of bone loss. Subjects were also required to have the permission of their treating physician to participate in sub-maximal physiological fitness testing and a moderate home-based progressive walking and resistance exercise program. Subjects were excluded if they

were osteoporotic (any t-score < 2.5), had taken bisphosphonates during the previous year, did not have physician permission (i.e. upper extremity lymphedema, or had a history of hypercalcaemia and/or kidney stones).

A randomized (block size of 8), open label, controlled, 2×2 factorial design was used. The four treatment groups were: 1) high-dose weekly calcitriol (ChromaDex), 2) an individualized home-based progressive walking and resistance exercise program (EXCAP), 3) a combination of both treatments, or 4) a daily multivitamin (control group; contained 400 IU of vitamin D and 200 mg of calcium) for 12 weeks.

Subjects were thoroughly screened to ensure their eligibility for the study. If deemed eligible and interested in participating, patients signed a consent statement. At the baseline visit, subjects underwent laboratory tests, completed paper questionnaires, and had a physical fitness examination. Participants' blood was drawn to determine serum levels of calcitriol, calcium, and bone metabolism biomarkers. Paper questionnaires completed by the participants included information on sociodemographics, fatigue, physical activity, and quality of life. Subjects underwent a physical fitness examination that assessed aerobic capacity, muscular strength, and body composition. Serum calcium was reassessed on day 3–6 and at week 6 to ensure participants were not hypercalcemic. At week 12, participants returned to repeat the same procedures performed in the baseline assessment.

Participants assigned to one of the calcitriol arms took 45 micrograms (mcg) of calcitriol once weekly. This dose was selected based on previous research that showed reduced hypercalcemia by using a weekly dosing strategy [5, 6, 8]. Participants were advised to increase their water intake by 3–4 cups on the day they took the calcitriol and on the following day. Because a 45 mcg dose of calcitriol was not commercially available, bulk calcitriol was purchased from ChromaDex (Irvine, CA). High-performance liquid chromatography (HPLC) was performed to ensure purity of the calcitriol, which was then compounded with almond oil, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) into single, 45 mcg capsules by the Investigative Drug Service (IDS) at the University of Rochester Medical Center. Calcitriol compliance was determined via pill count at follow-up.

The home-based aerobic and progressive resistance exercise program, EXCAP[®], was designed by a certified exercise scientist from the American College of Sports Medicine (ACSM) and adhered to the ACSM guidelines for exercise testing and prescription [2]. EXCAP[®] is an individualized, standardized, copyrighted intervention, modified to best target bone metabolism. The intervention was provided to the patient via a single, 45-minute, instructional session with the study coordinator, a Masters'-trained exercise physiologist, and each patient in the exercise arms received a prepackaged individual "exercise kit." The kit contained all of the materials necessary for the patient to complete the home-based walking and resistance band exercise intervention, including written instructional materials, a pedometer, and therapeutic resistance bands. The aerobic and resistance components of the home-based exercise program followed the guidelines described below.

The first component was an individually tailored walking prescription intended to provide moderately intense aerobic exercise (60%–70% of heart rate reserve, 3–5 exercise rating of perceived exertion on the ACSM revised rating scale—a visual analog scale ranging from 0 = no exertion at all to 10 = very, very strong: maximal exertion) 7 days a week for the entire 12-week exercise intervention time period. A pedometer was given to all exercise subjects during the baseline assessment period. Using the pedometer, subjects were instructed to record the number of steps they walked daily for one full week. Using the baseline average number of steps walked daily, patients in the home-based exercise intervention arms were instructed to increase their total steps walked each day by 5% to 10% each week until they reached a 12,000 steps/day maximum while maintaining a moderate intensity during the 12-week intervention.

The second component of the exercise program, an individually tailored therapeutic resistance band exercise prescription, was designed to provide a moderately intense progressive resistance exercise (5–8 exercise rating of perceived exertion on the ACSM revised rating scale) 3 days a week (with at least 1 day of rest in between) for the entire 12-week period to maintain muscle strength in the upper and lower body. The exercise physiologist thoroughly explained the proper use of the resistance bands and the appropriate mechanics for safely performing the resistance exercises while also providing an individualized progression plan for increasing sets, increasing repetitions, and changing band colors

Subjects were instructed to begin with an individually determined number of sets (1 set = 7–10 repetitions) for each of the 10 exercises (i.e., squats, side bends, leg extensions, leg curls, chest press, rows, toe raises, overhead press, biceps curls, triceps extensions). Patients were instructed to increase the intensity by changing the band color or shortening the initial length of the band for increased resistance. Patients were instructed to progressively increase from their individual baseline sets and repetitions to a maximum of 3 sets of 7–10 repetitions for each exercise daily over the course of the 12-week intervention at an optimally challenging rate.

Measures

On-study and clinical record forms: Demographic information obtained included age, menopausal status, gender, race, partnered status, job status, and educational background. Relevant medical information included height, weight, stage at diagnosis, and cancer treatment history.

Functional Measures

Osteoclasts, bone resorbing cells, remove old bone through a process called resorption. This study used serum levels of cross-linked *N*-telopeptides of type I collagen (NTx) to assess bone resorption. As a bone marker, NTx responds to therapy more rapidly than bone densitometry and independently predicts fracture risk [13, 42, 44]. After bone resorption, bone-forming cells called osteoblasts fill the area with a material called osteoid, which becomes fully mineralized bone. To measure bone formation, this study used bone-specific alkaline phosphatase (BSAP), a byproduct of osteoblast activity, which independently

predicts fracture risk [34]. Fasting-state blood samples were collected in plain red-top tubes at baseline and at 12 weeks. Blood samples were allowed to clot for 30 minutes and were then centrifuged to obtain serum. Serum samples were then aliquoted and stored at -80°C . Serum NTx levels were determined using an enzyme-linked immunosorbent assay and a specific monoclonal antibody for NTx (osteomark serum NTx). The intra-assay and interassay coefficients of variation for the NTx assay are 4.6% and 6.9%, respectively. Serum BSAP levels were determined by the Ostase® BAP Immunoenzymetric Assay. The intra- and inter-assay coefficients of variation for the BSAP assay are 6.4% and 6.5%, respectively.

To investigate the balance between bone formation and bone resorption, we used the formula proposed by Eastell et al to calculate a bone remodeling index (BRI) [16]. The formula is: $Z_{\text{BSAP}} - Z_{\text{NTx}}$, where $Z_{\text{BSAP}} = (\text{BSAP}_{\text{Observed}} - \text{BSAP}_{\mu} \text{ at baseline}) / \sigma$ (standard deviation) at baseline, and $Z_{\text{NTx}} = (\text{NTx}_{\text{Observed}} - \text{NTx}_{\mu} \text{ at baseline}) / \sigma$ at baseline. A positive number for the BRI indicates a net bone gain: i.e., resorption decreased and formation increased over the course of the intervention. A negative number for the BRI indicates net bone loss: i.e., resorption increased and formation decreased over the course of the intervention.

Statistical analyses

Analyses were performed with IBM SPSS Statistics Version 24. Clinical and demographic variables were examined with two-tailed ($\alpha = 0.05$) t-tests for continuous variables and chi-square tests for categorical variables to check for population differences in the four arms. Bone biomarkers were assessed using an analysis of covariance (ANCOVA) model with the arm assignment as the factor of interest and with the corresponding baseline bone biomarker level, menopausal status, hormone therapy (tamoxifen or aromatase inhibitor), and stage (0/I or II/III) as covariates. A main effects analysis was used for this study. This was done due to small numbers in each group and high level of variability among the bone biomarkers. By using a main effects analysis, we are able to better estimate potential effect sizes. ANCOVA models were used to test the main effects of active vitamin D and exercise using the same covariates, and 95% confidence intervals were computed for these effects. The assumption of no statistical interaction between active vitamin D and exercise was examined by adding the appropriate interaction term to the above model and testing for its significance. All data were analyzed using the intent-to-treat principle. Analyses were based on complete cases, because a sensitivity analysis revealed results were similar for both imputation and non-imputation methods.

Results

The treatment groups were similar at baseline with regard to demographic and clinical variables (Table 1). The average age at entry was 53.5 ± 7.8 (mean $\pm$ SD) years. The majority of participants were Caucasian (93%), postmenopausal (63%), and married (80%). Distribution was similar for type of hormone therapy (tamoxifen=51% vs AI=49%) and stage at diagnosis (stage 0/I=43% vs. stage II/III=57%). Approximately 60% of participants reported currently engaging in cardiovascular exercise at the start of the study, while less

than 20% reported engaging in resistance training. All participants received prior radiotherapy (100%) and the majority received chemotherapy (65%).

The flow of participants is illustrated in Figure 1. There were no significant differences among treatment groups in the proportion of participants who completed the study on their assigned treatments. A total of three subjects did not complete the trial: two subjects withdrew consent, and one subject was withdrawn at the discretion of the Principal Investigator. None of the participants withdrew from the study because of adverse events.

Adverse events by group are reported in Table 2. Subjects assigned to one of the calcitriol groups had 3 instances of hypercalcemia, all of which were grade 1, compared to no cases of hypercalcemia in the groups that did not receive calcitriol. There were no instances of any grade 3 adverse events in the study and only one instance of a grade 2 adverse event (hyperglycemia in the control group). Rates of creatinine elevation, hyperkalemia, hyponatremia, hyperglycemia, and blood urea nitrogen elevation were similar between groups.

Compliance in the calcitriol groups was measured via pill count; 17 of the 19 subjects assigned to calcitriol took 100% of scheduled doses, and 2 subjects took 83.3% of scheduled doses. Compliance with the walking intervention was optimal, as 100% of subjects in the exercise group self-reported increased walking. Walking compliance was assessed based on the number of minutes per week spent walking. At baseline, subjects in the exercise group reported walking an average of 116 minutes/week for physical activity. At follow-up, subjects in the exercise group increased their walking time to 150 minutes/week. At baseline, 3 out of 21 (14.3%) subjects assigned to one of the exercise groups reported engaging in resistance training. At follow-up, 8 of 18 (44.4%) subjects in the exercise groups reported performing resistance training. Of those who reported engaging in resistance training at follow-up, the average time spent was 110 minutes/week.

Table 3 shows the change in fitness measures from baseline to follow-up at week 12 by main effects analysis. Those assigned to the exercise group had an average daily step count of 7,319 at baseline and 8,747 steps per day at follow-up, reflecting an increase of 1,428 steps daily. There were no differences between the calcitriol and no calcitriol groups in changes in VO2max, handgrip strength, chest press, and leg extension. For the exercise group, there were improvements in VO2max (+2.13 mL/kg/min; $p=0.22$), handgrip strength (+0.96 kg; $p=0.16$), and chest press (+2.63 kg; $p=0.38$), but these improvements were not significantly greater than in the non-exercise group.

The results of the change in bone metabolism biomarkers are shown on Table 4. Overall, there were no differences at baseline for bone resorption (NTx), bone formation (BSAP), and the bone remodeling index (BRI) across all groups. Bone resorption increased slightly for exercise (+1.10 nm Bone Collagen Equivalent [BCE]) and no exercise (+1.37 nm BCE) groups, with no significant difference between the two groups (Cohen's $d=0.13$; $p=0.86$). Similarly, bone formation marginally increased in the exercise group (+1.96 ng/ml) compared to the no exercise group (+1.10 ng/ml), but the difference was not significant

(Cohen's $d=0.13$; $p=0.49$). Changes in the BRI were similar for the exercise (+0.06) and no exercise groups (+0.01; Cohen's $d=0.14$; $p=0.83$).

Bone resorption increased for the calcitriol group (+2.38 nm BCE), but the difference was not significant compared to the no calcitriol group (+0.01 nm BCE; Cohen's $d=0.31$; $p=0.19$). The calcitriol group had a large, statistically significant increase in bone formation (+3.56 ng/ml) versus the no calcitriol group (-0.68 mg/ml; Cohen's $d=0.64$; $p<0.01$). This increase resulted in an increase in BRI for the calcitriol group (+0.16), while there was a decrease in BRI for the no calcitriol group (-0.09), although this difference was not significant (Cohen's $d=0.21$; $p=0.31$).

Discussion

In this pilot trial of high-dose weekly calcitriol and an individualized exercise program, we found both exercise and calcitriol were well tolerated and feasible for breast cancer survivors on hormonal therapy. This study is one of the first to employ a weekly, high-dose calcitriol regimen to improve bone health in cancer patients on hormonal therapy. Only three subjects did not complete the study, and they were equally dispersed among the groups. Compliance with calcitriol therapy was optimal with 89% of subjects taking all of their scheduled doses. Hypercalcemia rates were also significantly lower than in other trials that employed a daily dosing regimen, in which hypercalcemia rates exceeded 50% [32]. Compliance with exercise was less than optimal. Subjects in the exercise groups increased their average daily steps from 7,319 at baseline to 8,747 steps per day at follow-up for an increase of 1,428 steps daily. This fell significantly short of our goal to increase steps between 5–10% per week for the duration of the trial. Furthermore, while subjects in the exercise group improved their VO₂max, handgrip strength, and chest press strength, the improvements were not significant compared to subjects who did not receive exercise.

In terms of efficacy, calcitriol therapy resulted in a significant increase in bone formation, as measured by BSAP, compared to subjects who did not receive calcitriol. This is considered a moderate effect size, with a Cohen's d of 0.64. There was an increase in the BRI for the calcitriol group and a decrease in BRI for the no calcitriol group, but this difference did not reach statistical significance. Exercise failed to favorably change bone resorption, bone formation, and BRI compared to the no exercise group.

The improvement in bone formation levels for the calcitriol group is in agreement with the results of other clinical trials that examined the effect of calcitriol therapy on bone formation [9, 10, 18, 19, 36]. Other studies reported significant decreases in bone resorption, [17, 35, 37] but this study failed to find such a reduction in resorption with calcitriol therapy. Despite the lack of effect on bone resorption, calcitriol improved the BRI, indicating bone formation exceeded bone resorption which results in a favorable change in bone metabolism. This study is fundamentally different than previous calcitriol trials, as the vast majority of those trials used a daily dosing strategy, while this study used a significantly higher dose that was administered once weekly. Using this dosing regimen, we were able to decrease the proportion and severity of hypercalcemia while significantly improving bone formation levels.

While other studies of exercise demonstrate beneficial effects on bone metabolism, this study did not find any beneficial effect on bone health. The lack of effect of exercise may be due to a lack of optimal adherence to the exercise intervention. While the exercise group increased their steps by an average of 1,428 steps per day, this fell well below the instructed increase of 5–10% per week until a maximum of 12,000 steps per day was reached. In addition, the lack of significant change in handgrip, chest, and leg strength indicates a lack of adherence to the resistance portion of the exercise intervention. It is also possible the exercises prescribed in the intervention had insufficient intensity to favorably increase bone metabolism. Lastly, the possibility remains that the intervention duration was insufficient to significantly alter bone metabolism levels, as a number of previous studies used 6- to 12-month intervention durations.

Further studies are needed to confirm these findings related to calcitriol. This is one of the first studies to test this type of dosing regimen, and trials of a longer duration with greater numbers of subjects are needed. However, there are limiting factors in conducting research with calcitriol using this type of regimen. First, calcitriol therapy requires increased monitoring due to the chance of developing hypercalcemia or hypercalciuria. Limiting calcium intake is an effective method of reducing hypercalcemia/hypercalciuria, but monitoring is still required. Next, larger calcitriol doses, such as the one used in this study, are not commercially available and require a compounding pharmacist. Furthermore, comparing calcitriol amounts to cholecalciferol is difficult with no accepted conversion. However, one recent publications found similar effects between 800 IU of cholecalciferol and 0.25 mcg of calcitriol [45], which would equate our 45 mcg dose of calcitriol to 144,000 IU of cholecalciferol. Despite the challenges, calcitriol remains a promising agent for improving bone health. The vast majority of pharmacologic bone agents are antiresorptive, and very few treatment options improve bone formation. It is possible that calcitriol therapy could be employed with antiresorptive agents, such as bisphosphonates and denosumab, to produce a greater benefit in terms of bone metabolism.

In summary, this is one of the first studies to show that weekly, high-dose calcitriol therapy significantly increased bone formation, resulting in a positive bone remodeling index. Exercise failed to improve bone metabolism, which may be due to a lack of adherence as judged by a lack of significant improvement in fitness measures. Further studies are needed to confirm these findings. Future studies may use this calcitriol regimen in conjunction with existing bone drugs to increase efficacy.

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CONSORT diagram showing the flow of participants through each stage of a randomized trial.

Figure 1.
Consort

Table 1

Baseline Characteristics

Variable	Control n=10	Exercise n=10	Calcitriol n=10	Combination n=11	p-value
Age					
48 years old	60.0%	10.0%	50.0%	18.2%	0.15
49–57 years old	20.0%	40.0%	20.0%	54.5%	
58 years old	20.0%	50.0%	30.0%	27.3%	
Menopausal Status					
Premenopausal (%)	60.0%	10.0%	50.0%	27.3%	
Postmenopausal (%)	40.0%	90.0%	50.0%	72.7%	0.09
Marital Status					
Married (%)	60.0%	70.0%	90.0%	100.0%	
Single/Divorced/Widowed (%)	40.0%	30.0%	10.0%	0.0%	0.10
Race					
White (%)	90.0%	100.0%	80.0%	100.0%	
Not White (%)	10.0%	0.0%	20.0%	0.0%	0.27
Body Mass Index (BMI)					
Mean (kg/m2)	28.4	32.4	28.1	31.3	0.29
Stage					
0/I (%)	30.0%	20.0%	50.0%	63.6%	
II (%)	40.0%	60.0%	40.0%	27.3%	
III (%)	30.0%	20.0%	10.0%	9.1%	0.42
Prior Chemotherapy					
Yes (%)	70.0%	70.0%	70.0%	54.5%	
No (%)	30.0%	30.0%	30.0%	45.5%	0.84
Prior Radiotherapy					
Yes (%)	100.0%	100.0%	100.0%	100.0%	
No (%)	0.0%	0.0%	0.0%	0.0%	1.00
Hormonal Therapy					
Tamoxifen (%)	70.0%	44.4%	60.0%	36.4%	
Aromatase Inhibitor (%)	30.0%	55.6%	40.0%	63.6%	0.42
Current Cardiovascular Exercise					
Yes (%)	50.0%	60.0%	60.0%	63.6%	
No (%)	50.0%	40.0%	40.0%	36.4%	0.93
Current Resistance Training					
Yes (%)	20.0%	0.0%	20.0%	27.3%	
No (%)	80.0%	100.0%	80.0%	72.7%	0.39
1, 25 (OH) ₂ Vitamin D					
pmol/L	60.8	120.7	83.9	69.7	0.34
NTx					
nm BCE	12.2	11.6	13.4	14.4	0.89
BSAP					
ng/ml	12.2	13.8	12.2	12.0	0.93
Bone Metabolism Index					
	0.03	0.34	−0.12	−0.26	0.72

Table 2

Adverse Events

	Calcitriol			No Calcitriol		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Hypercalcemia	3	0	0	0	0	0
Creatinine elevation	0	0	0	0	0	0
Hyperkalemia	1	0	0	1	0	0
Hypernatremia	0	0	0	1	0	0
Hyperglycemia	3	0	0	5	1	0
Blood Urea Nitrogen elevation	4	0	0	4	0	0

Fitness Testing

Table 3

	No Exercise	Exercise	p-value	No Calcitriol	Calcitriol	p-value
VO2max (mL/kg/min) Final	22.6	24.0		23.5	23.1	
VO2max (mL/kg/min) Change	0.80	2.13	0.22	1.68	1.28	0.76
Handgrip (kg) Final	26.6	27.8		27.4	27.1	
Handgrip (kg) Change	-1.46	0.96	0.16	-0.21	-0.30	0.84
Chest Press (kg) Final	54.2	55.9		56.1	54.5	
Chest Press (kg) Change	0.94	2.63	0.38	2.88	1.24	0.38
Leg Extension (kg) Final	46.38	47.38		45.70	47.74	
Leg Extension (kg) Change	1.90	2.89	0.79	1.22	3.26	0.60
BMI (kg/m ²) Final	30.0	30.2		30.1	30.1	
BMI (kg/m ²) Change	0.07	-0.16	0.38	0.07	0.04	0.92

Table 4

Bone metabolism biomarkers

		No Exercise	Exercise	Cohen's d	p-value
NTx Baseline	nm BCE	12.8	13.0		0.95
NTx Final *	nm BCE	14.3	13.3		0.86
NTx Change *	nm BCE	1.37	1.10	0.13	0.86
BSAP Baseline	ng/ml	12.2	12.9		0.75
BSAP Final *	ng/ml	13.8	14.7		0.49
BSAP Change *	ng/ml	1.10	1.96	0.13	0.49
Bone Remodeling Index Baseline		-0.04	0.06		0.80
Bone Remodeling Index Final *		0.12	0.17		0.83
Bone Remodeling Index Change *		0.01	0.06	0.14	0.83
		No Calcitriol	Calcitriol	Cohen's d	p-value
NTx Baseline	nm BCE	11.9	13.9		0.46
NTx Final *	nm BCE	12.5	15.0		0.19
NTx Change *	nm BCE	0.01	2.38	0.31	0.19
BSAP Baseline	ng/ml	13.0	12.1		0.66
BSAP Final *	ng/ml	12.0	16.3		<0.01
BSAP Change *	ng/ml	-0.68	3.56	0.64	<0.01
Bone Remodeling Index Baseline		0.19	-0.18		0.33
Bone Remodeling Index Final *		0.02	0.26		0.31
Bone Remodeling Index Change *		-0.09	0.16	0.21	0.31

* Adjusted for corresponding baseline values