ORIGINAL ARTICLE

Bone-loading exercises versus risedronate for the prevention of osteoporosis in postmenopausal women with low bone mass: a randomized controlled trial

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Abstract

Purpose This randomized controlled trial compared changes in bone mineral density (BMD) and bone turnover in postmenopausal women with low bone mass randomized to 12 months of either risedronate, exercise, or a control group.

Methods Two hundred seventy-six women with low bone mass, within 6 years of menopause, were included in analysis. Treatment groups were 12 months of (a) calcium and vitamin D supplements (CaD) (control), (b) risedronate + CaD (risedronate), or (c) bone-loading exercises + CaD (exercise). BMD and serum markers for bone formation (Alkphase B) and resorption (Serum Ntx) were analyzed at baseline, 6, and 12 months.

Results Using hierarchical linear modeling, a group by time interaction was found for BMD at the spine, indicating a greater improvement in the risedronate group compared to exercise ($p \le .010$) or control groups ($p \le .001$). At 12 months, for women prescribed risedronate, changes in BMD at the spine, hip, and femoral neck from baseline were + 1.9%, + 0.9%, and + .09%; in exercise group women, + 0.2%, + 0.5%, and − 0.4%; and in control group women, − 0.7%, + 0.5%, and − 0.5%. There were also significant differences in reductions in Alkphase B (RvsE, $p < .001$, RvsC, $p < .001$) and Serum Ntx (RvsE, $p = .004$, RvsC, $p = .007$) in risedronate women compared to exercise and control groups. For risedronate, 12-month changes in Alkphase B and Serum Ntx were − 20.3% and − 19.0%; for exercise, − 6.7% and − 7.0%; and for control, − 6.3% and − 9.0%.

Conclusion Postmenopausal women with low bone mass should obtain adequate calcium and vitamin D and participate in bone-loading exercises. Additional use of BPs will increase BMD, especially at the spine.

Keywords Postmenopausal women · Low bone mass · Risedronate · Bone-loading exercises · Bone mineral density (BMD) · Bone formation and resorption

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Introduction

Osteoporosis, characterized by bone loss (low bone mineral density [BMD], alterations in bone structure) and resultant fractures, is a major health problem of crisis proportions in postmenopausal women [1–3]. Postmenopausal women with fractures experience a decrease in quality of life and increased financial burden due to cost of care, and after an osteoporotic hip fracture, the 1-year mortality rate is approximately 21% [4, 5]. According to the National Osteoporosis Foundation (NOF), 43 million postmenopausal women in the USA have low bone mass (T-score − 1 to − 2.49) and are at risk for osteoporosis (< − 2.5) [1, 4]. Preserving and improving BMD in these patients are critical. Compared to patients with low bone mass, patients with osteoporosis have a twofold higher risk of developing fractures [6].

Calcium and vitamin D supplementation, lifestyle modifications such as smoking cessation, prevention of falls, and exercises are recommended for all women with both low bone mass and osteoporosis [3, 7]. Bisphosphonates (BPs) such as risedronate have been found to be effective in improving BMD and preventing fractures and are considered first line-treatment for women with osteoporosis [7]. Women with low bone mass can also be prescribed BPs [7, 8]. However, prescribing BPs for women with low bone mass who do not yet have osteoporosis has been controversial. This controversy is related to the rare incidences of adverse effects (AEs) with long-term use of BPs, such as development of atypical femoral fractures [9, 10].

Participating in weight-bearing plus resistance training (bone-loading) exercises has also been shown to improve BMD and prevent fractures in postmenopausal women at risk for bone loss [11–14]. Results of this present study can inform decision-making as to whether postmenopausal women with low bone mass can be prescribed bone-loading exercises in place of medication. This study compared changes in BMD and biomarkers of bone turnover in postmenopausal women with low bone mass randomized to either 12 months of the BP "risedronate," bone-loading exercises, or a control group of women obtaining calcium and vitamin D supplements only. The following are study aims:

Aim 1: To compare changes in BMD at the total hip, femoral neck, and spine (dual-energy X-ray absorptiometry [DXA]) in control, risedronate, and exercise group participants after 6 and 12 months of treatment.
Aim 2: To compare changes in biomarkers of bone formation and resorption in control, risedronate, and exercise group participants after 6 and 12 months of treatment (formation: Alkphase B, resorption: Serum Ntx).
Aim 3: To describe women's reports of adverse effects (AEs) to treatments as well as 12-month adherence to prescriptions for bone-loading exercises and risedronate. *Research question related to Aim 3*: Were there relationships between adherence rates to exercises or to risedronate and changes in BMD and serum biomarkers of bone turnover after 12 months of the treatment?

Background and significance

While women are encouraged to engage in exercise to improve bone health, clinicians are reluctant to prescribe the more intensive bone-loading exercises due to concerns about safety with exercises, women's adherence to exercises, and the effectiveness of the exercises [14].

The LIFTMOR (Lifting Intervention for Training Muscle and Osteoporosis Rehabilitation) clinical trial was one of the first studies to address these clinicians' concerns [14]. Results of this study were that 8 months of 30-min, twice-weekly, supervised high-intensity resistance and impact training were safe for postmenopausal women with low bone mass, were effective in improving BMD, and most women were adherent to the program. In the LIFTMOR study, after 8 months of exercise, BMD at the lumbar spine increased by 2.9% ($SD = 3.1$, $p < 0.001$) and BMD at the femoral neck increased by 0.3% ($SD = 3.0$, $p = 0.025$) [14].

Our study builds on the LIFTMOR clinical trial and adds further data to inform whether postmenopausal women with low bone mass can effectively maintain or even improve BMD with bone-loading exercises prior to prescriptions for medication. Our long-term goal is to contribute to the development of clinical practice guidelines for the prevention of fractures in postmenopausal women with low bone mass.

Clinical management pathways for women who are at risk for other chronic illnesses such as hypertension or diabetes include trials of lifestyle modifications prior to prescriptions for medications. Thus, due to the potential for adverse effects with long-term use of BPs, the significant consequences of progression to osteoporosis, and the potential bone strength and fracture reduction benefits of exercise, we proposed conduct of our study to determine if, in women with low bone mass, prescriptions for exercises are warranted prior to prescriptions for medications. If an effective exercise program could substitute for or delay the use of BPs such as risedronate in post-menopausal women with low bone mass, not only would bone health improve throughout the lifespan, but women would also benefit from the many other positive effects of exercise.

Methods

Approvals

Data for this study were collected in a larger study entitled: *Bone Loading Exercises versus Risedronate on Bone Health in Post-menopausal women* supported by the National Institute of Nursing Research under award number R01NR015029. The study was approved by the Institutional Review Boards at both the University of Nebraska and Creighton University Medical Centers, as both were involved in implementation of the study. Written consent for participation and publication of data were obtained from participants at the time of enrollment. Participants received informed consent documents for review prior to their enrollment visit. Careful and thorough explanations were utilized in obtainment of consent to ensure participant comprehension. The R01 study is registered as a clinical trial under the title: Heartland Osteoporosis Prevention Study (see https://clinicaltrials.gov).

Design

We used a prospective stratified (by exercise history), randomized, 3-group repeated measures experimental design with three major data collection points (baseline, 6, and 12 months).

Sample

The power analysis for sample size was based on a small and conservative effect size of $f = 0.15$ and conducted using G*Power 3 [15]. For a repeated measures analysis of variance, a significance level of 0.05 was assumed for the three time points, with an estimate of 0.5 for the correlation between time points. We believed a sample of 246 participants across three groups would provide sufficient evidence to detect the effects of interest in study calculations. To account for up to 20% attrition, the optimal enrollment goal was 302 participants. We enrolled 276 participants in our study. Data from all 276 women were included in this intent-to-treat analysis.

Women were included in the study if they had low bone mass (*T*-score of -1.0 to 2.49), were in their first 6 years after a diagnosis of menopause and had their health care provider's approval to be in the study. Menopause was diagnosed as women having no menstrual period for the last 12 months; time of menopause was determined as 12 months after the date when women reported their last menstrual period [16].

Women were excluded from the study if they had a diagnosis of osteoporosis (*T*-score < -2.5); had an increased risk of a major or hip fracture; had been on BPs within the last 6 months; were currently on estrogen, tamoxifen, or aromatase inhibitors; had a serum vitamin D level < 10 mg/ml or > 100 mg/ml; had any conditions that prohibited prescriptions for calcium and vitamin D supplements, risedronate, or exercise; or weighed more than 300 lbs. An increased risk of a major or hip fracture was defined as a Fracture Risk Assessment (FRAX) score indicating a 10-year hip fracture probability $\geq 3\%$ or a 10-year probability of a major osteoporotic fracture $\geq 20\%$. FRAX scores are determined by factors such as age, sex, weight, height, previous fracture, a parent with a fractured hip, currently smoking, on glucocorticoids, alcohol abuse, presence of medical conditions related to secondary osteoporosis, and femoral neck BMD [17, 18]. Women over 300 lbs. were excluded because results of DXA testing with Hologic machines for these women would not be accurate.

Women of all races and ethnicities were encouraged to participate in this study, and participants were recruited through practitioner referral, community presentations, distribution of flyers, postcard mailings, and generation of a website and Facebook page [19].

Randomization

This study used a statistician-generated procedure for randomization to control, risedronate, or exercise groups, and stratification was by exercise history. Prior to randomization, participants reported their usual levels of exercise (≥ 2 high intensity exercise sessions per week; < 2 sessions per week) to ensure equal distribution among groups. Both participants and team members were blinded to group assignment at the time of subject enrollment. After enrollment, participants and research team members learned group assignment by opening a sealed, opaque envelope.

Setting

All BMD testing, blood draws, and participant interviews were completed at the Creighton University Osteoporosis Research Center (CORC) in Omaha, NE. Participants randomized to the exercise group completed the exercise program at community fitness centers in Omaha and Lincoln, NE.

Study treatments

Calcium/vitamin D

The National Osteoporosis Foundation (NOF) recommends that women over age 50 consume 1200 mg of calcium and

800–1000 IU of vitamin D_3 per day—either from their diet or from supplements [1]. In our study, dietary intakes of calcium at baseline were calculated for all women using the National Osteoporosis Foundation (NOF) Calcium Intake Estimate. Based on dietary intakes, calcium citrate supplements were prescribed to ensure subject's total daily intake (dietary and supplemental) was ~ 1200 mg [1]. Participants were prescribed doses of vitamin D based on their serum 25(OH) D levels at baseline, with the goal of women reaching and maintaining a serum level of at least 30 ng/ml [1]. Participants who had serum D levels at 30 ng/ml or greater were prescribed 1000 IU daily, levels of 20–29 ng/ml were prescribed 2000 IU, and levels of 10–19 ng/ml were prescribed 3000 IU. Serum D levels were rechecked at 6 months, and prescriptions were revised as needed.

Risedronate

Risedronate sodium is a pyridinyl bisphosphonate which inhibits osteoclast-mediated bone resorption, thus indirectly increasing BMD [7]. Participants randomized to the risedronate group took the prescribed calcium and vitamin D supplements daily and a 150 mg tablet of oral risedronate once every 4 weeks for 12 months.

Bone-loading exercise program

Bone-loading exercises were 3-times weekly and included jogging using a weighted vest and resistance exercises of the major muscle groups under the direction of the study exercise training and designated exercise trainers at fitness centers (on-site ETs). One Repetitive Maximum (1RM) estimation tests were conducted at baseline and 6 months, and initial weight settings and reps and sets for women were determined by the 1RM or volitional fatigue at 8–12 repetitions. On-site ETs met with women every two weeks during the 12-month study to discuss expected weight loads, reps, and set progressions. Participants were not supervised during sessions; however, there were always ETs available in the fitness centers to respond to questions and concerns. A more detailed exercise protocol and progression program is described in Bilek (2016) [20].

Steps to promote intervention fidelity

Three research team members in addition to principal investigators conducted all procedures for obtaining informed consent and administering interventions. One research exercise trainer had overall responsibility for the exercise intervention and for supervision of the on-site exercise trainers at the five fitness centers—two in Lincoln and three in Omaha. Training sessions were held with research team members

and on-site exercise trainers prior to implementing the study to standardize administration of interventions across sites.

Study outcome measures: BMD, serum biomarkers of bone turnover, adherence rates

Outcomes for the study were bone structure measures-peripheral quantitative computed tomography (pQCT) at the tibia and Hip Structural Analysis (HSA); BMD at the total hip, femoral neck, and spine (Hologic QDR2000™ DXA); and serum biomarkers of bone formation (Alkphase B) and resorption (Serum Ntx). In addition, adherence rates and adverse effects were examined for women in all three treatment groups. This report focuses only on outcomes for BMD and biomarkers of bone turnover. Changes in bone structure in groups will be described in a second article soon to be published.

For measuring BMD using DXA scans, patients are irradiated at specific sites (most often the hip and spine) with an X-ray beam of two different energies, enabling bone attenuation to be separated from soft tissue attenuation [21]. In our study, all participants used the same machine throughout, tests were performed by technicians certified in densitometry testing, and all results were interpreted by one research team radiologist.

Rates of bone resorption and formation were measured with Serum Ntx and Alkphase B. Serum was drawn by team members certified in phlebotomy training and/or who had many years of experience with phlebotomy, and serum tests were analyzed by technicians with experience in serum biomarker testing and with ELISA.

Adherence to exercise was defined as the number of sessions women attended at the fitness center/the number of sessions prescribed. Attendance at sessions and AEs with exercises were documented by women in their exercise log and by on-site ETs in their bimonthly documentation forms. Adherence to calcium, vitamin D, and risedronate were measured by pill counts. Women reported AEs with risedronate and supplements by completing investigator-developed forms at 3, 6, and 12 months, or by personal contact with research team members [20].

Study variables, instruments, outcome measures, and data collection time points are included in Table 1.

Data analysis

All statistical analyses were performed using IBM SPSS Version 25. Data were double-entered and inspected for artifacts, missing or out of range values and normality. Consistent with intent to treat analysis, data from all 276 participants were included in this hierarchical linear modeling analysis. All available data were used and there was no data imputation [15]. The primary outcomes of BMD, Alkphase

Table 1 Study variables, instruments, and rationale for use in this report

Measure	Purpose	B	6	12
Demographic profile and health history	Demographic data and medical history to describe sample and identify potential covariates	x		
Calcium, PTH, 25(OH)D, TSH, creatinine (Cr)	To identify abnormalities which exclude participation, and serum Vit D informs prescription for dosage of Vit D	x		
Serum measures of Alkphase B and Serum NTx	To describe changes in rate of bone formation and bone absorption over time	x	x	x
NOF calcium intake estimate	Calculates dietary intake of calcium based on servings of calcium-rich food per day	x		
Fracture Risk Assessment Tool (FRAX)	Estimates 10-year risk of osteoporotic fracture	x		
Incidence of Fractures Documentation Form	Incidence, type, cause, treatment of fracture	x	x	x
Adherence to CaD, risedronate, exercises [29]	Documentation of unused tablets in individual bubbles of returned medication cards as well as documentation of exercise sessions attended in exercise logs and daily logs at fitness centers	x	x	x
Self-reported adverse effects	Completed by participants on investigator-developed data collection forms or reported to on-site ETs of research team members during participant visits		x	x
DXA	BMD at total hip, femoral neck, and spine	x	x	x
1RM	Maximum weight lifted once through full range of motion (ROM) to measure muscle strength	x	x	

Abbreviations: *DXA* dual-energy X-ray absorptiometry, *IRM* one repetition maximum; *NOF* National Osteoporosis Foundation, *PTH* parathyroid hormone, *TSH* thyroid stimulating hormone, *CaD* calcium + vitamin D supplements

B, and Serum Ntx were compared between groups and over time. A significant time-group interaction would indicate that the three groups being compared had significantly different outcomes at 12 months [15]. Relationships between adherence rates to risedronate and exercises and changes in BMD at 12 months were analyzed using correlations, and AEs associated with risedronate and exercises were examined with descriptive statistics.

Results

Study sample

Figure 1 is a CONSORT diagram depicting the flow of participants' progress through the study. Demographic variables and BMD *T*-scores at baseline for women randomized to the three groups are described in Table 2. Baseline variables for the three groups of women were compared using analysis of variance and chi-square tests, and there were no significant differences in variables based on group.

Although data from all 276 women were used in this intent-to-treat analysis, 49 of the 276 women withdrew during the study, and only 227 women completed 12-month testing (see Fig. 1). Fourteen of the women were involuntarily withdrawn because they no longer met inclusion criteria for the study (e.g., they were diagnosed with osteoporosis at six months), and 35 women voluntarily withdrew from the study for reasons such as "they experienced AEs from treatment, or they believed they had no time to exercise." Compared to the 49 women who withdrew, the 227 women

retained in the study were older ($p = 0.032$); were married ($p = 0.026$); and had a greater increase in BMD at the spine at 6 months ($p = 0.02$).

All other results were organized to respond to the aims of the study.

Aim 1: To compare changes in BMD at the total hip, femoral neck, and spine (dual-energy X-ray absorptiometry [DXA]) in control, risedronate, and exercise group participants after 6 and 12 months of treatment.
BMD at the spine significantly improved ($p < 0.001$) over time (baseline to 12 months) in the risedronate group and did not change in control or exercise groups. Based on hierarchical linear modeling analysis, a group by time interaction was found for BMD at the spine, indicating a greater improvement at the spine in the risedronate group compared to exercise ($p \leq 0.010$) or control groups ($p \leq 0.001$). There were no significant differences in changes in BMD based on assignment to exercise or control groups. At 12 months, for women prescribed risedronate, the changes in BMD at the spine, hip, and femoral neck from baseline were + 1.9%, + 0.9%, and + 0.09%; in exercise group women, + 0.2%, + 0.5%, and − 0.4%; and in control group women, − 0.7%, + 0.5%, and − 0.5% (see Table 3).
Aim 2: To compare changes in biomarkers of bone formation and resorption in control, risedronate, and exercise group participants after 6 and 12 months of treatment (formation: Alkphase B, resorption: Serum Ntx).
Using hierarchical linear modeling, there were significant differences in reductions in Alkphase B (RvsE,

Fig. 1 CONSORT flowchart.
Abbreviations: WD, withdrew;
ITT, intent-to-treat
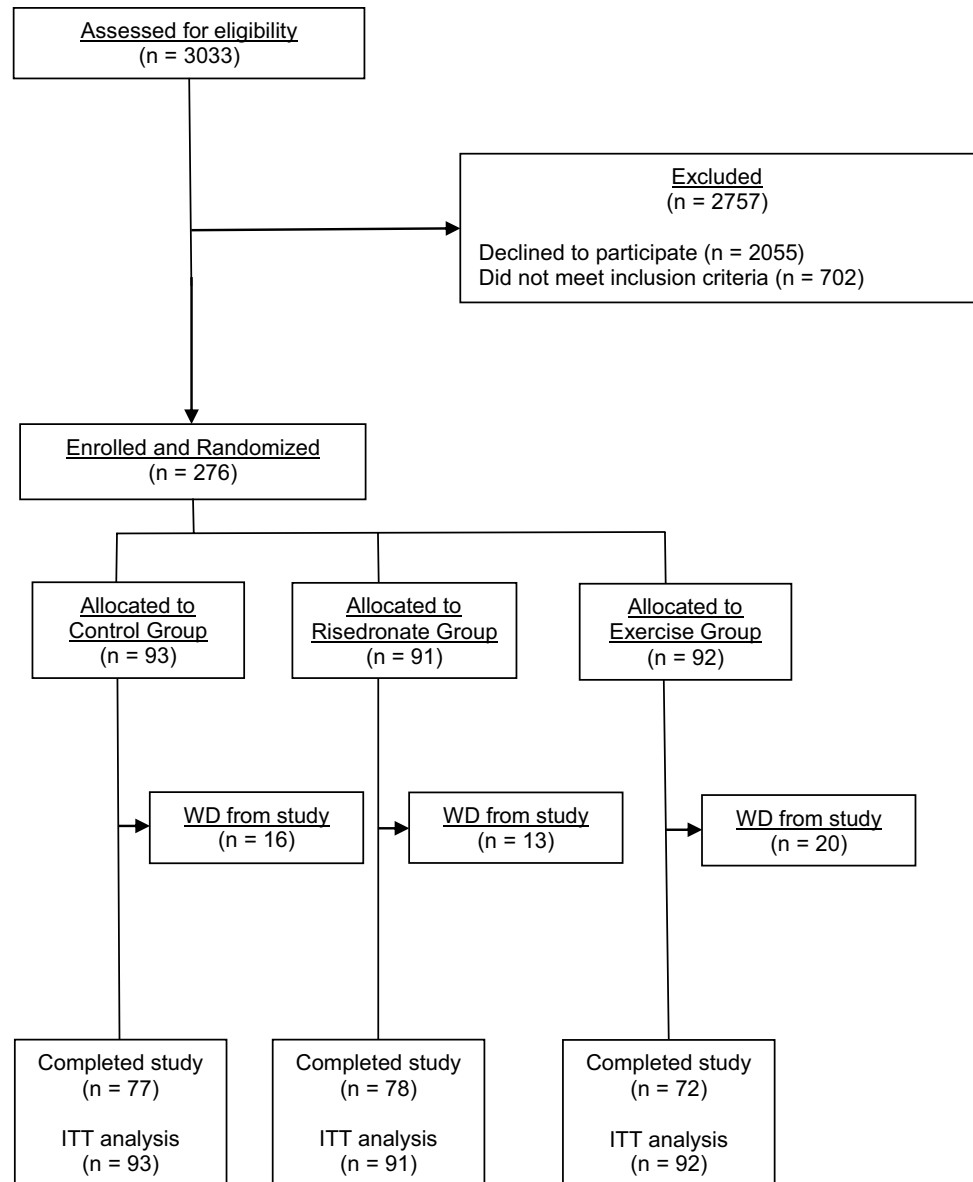
$p < 0.001$, RvsC, $p < 0.001$) and Serum Ntx (RvsE, $p = 0.004$, RvsC, $p = 0.007$) in risedronate women compared to women in exercise or control groups. There were no significant differences in reductions in Serum Ntx and Alkphase B based on assignment to exercise or control groups. For women prescribed risedronate, percent changes in Alkphase B and Serum Ntx from baseline were -20.3% and -19.0%; in exercise group women, -6.7% and -7.0%; and in control group women, -6.3% and -9.0% (see Table 4).

Aim 3: To describe women's reports of adverse effects (AEs) to treatments as well as 12-month adherence to prescriptions for bone-loading exercises and risedronate. The most frequent AE for calcium supplements was constipation ($n = 7$). Women with constipation dis-

continued their supplements and reported that they increased their dietary intake of calcium to measures of approximately 1200 mg daily. Women taking rise-dronate reported gastrointestinal (GI) disturbances ($n = 4$), muscle or joint pain ($n = 11$), and chest pain or dizziness ($n = 2$, and nine of these 17 women who had AEs did discontinue use of risedronate. All women with adverse effects to risedronate did report that their symptoms no longer occurred once they had discontinued the medication. No women complained of adverse effects with vitamin D. A few women complained of muscle soreness with exercises. Adaptations were made in their exercise schedules, and these women were able to continue to exercise. None of the women in the exercise group experienced a serious injury or fracture due to

Table 2 Sample characteristics at baseline based on group assignment (n = 276)

Baseline characteristics	Control (n=93) Mean (SD)	Risedronate (n=91) Mean (SD)	Exercise (n=92) Mean (SD)
Age (years)	54.3 (3.3)	54.5 (3.0)	54.4 (3.1))
BMI	25.9 (5.2)	25.2 (4.3)	25.9 (4.3)
Months since menopause	46.7 (29.8)	48.7 (41.0)	50.4 (49.5)
Has daily calcium intake of at least 1200 mg., and serum measures of 25(OH)D of at least 30 ng/ml			
Calcium intake per day (mg)	14% (15.2)	21% (23.6)	19% (20.7)
Serum 25 (OH) D (ng/ml)	75% (81.5)	74% (81.3)	74% (81.3)
Race/ethnicity			
Number (%)			
Caucasian/not Hispanic	79 (84.9%)	74 (81.3%)	77 (83.7%)
Caucasian/Hispanic	8 (8.6%)	6 (6.6%)	3 (3.3%)
Asian	1 (1.1%)	5 (5.5%)	2 (2.2%)
African American	2 (2.2%)	2 (2.2%)	1 (1.1%)
American Indian	1 (1.1%)	0	1 (1.1%)
Mexican	2 (2.2%)	4 (4.4%)	8 (8.6%)
BMD *T*-scores			
Lumbar spine	− 1.49 (0.62)	− 1.44 (0.54)	− 1.44 (0.61)
Total hip	− 0.95 (0.55)	− 0.91 (0.56)	− 0.78 (0.61)
Femoral neck	− 1.47 (0.63)	− 1.39 (0.62)	− 1.28 (0.66)
Marital status			
Number (%)			
Married—yes	71 (76.3%)	70 (76.9%)	66 (71.1%)
Single/divorced—yes	21 (22.6%)	19 (20.9%)	26 (28.2%)
Currently smoking			
Number (%)	1 (1.1%)	3 (3.3%)	1 (1.1%)
Has chronic ailments			
Number (%)	16 (17.2%)	18 (19.8%)	11 (12.0%)
Has family history of osteoporosis or osteopenia			
Number (%)	57 (61.3%)	52 (57.1%)	53 (57.6%)
Highest educational level			
Number (%)			
Less than college degree	19 (20.4%)	25 (27.5%)	15 (16.3%)
4-year college degree	52 (55.9%)	38 (41.8%)	54 (58.7%)
Masters	14 (15.1%)	22 (24.2%)	20 (21.7%)

Abbreviations: *Serum 25 (OH) D* serum measure of 25-hyroxyvitamin D, *BMI* body mass index

exercises. A greater number of women in the exercise group did withdraw from the study (n = 20) compared to women in control (n = 16) or risedronate (n = 13) groups. Women reported that they did not withdraw because of AEs from exercise, rather they believed they had no time to continue exercising (see Waltman, 2021 [22]).

Research question related to Aim 3: Were there relationships between adherence rates to exercises or to risedronate and changes in BMD and serum biomarkers of bone turnover after 12 months of the treatment?

For the 227 of 276 participants who remained in the study and completed 12-month testing, 12-month adherence to calcium was 92.0% (SD = 19.1); vitamin D, 94.2% (SD = 13.5); risedronate, 74.9% (SD = 39.5); and exercises, 58.9% (SD = 27.2). For women in the risedronate group, increased adherence rates to risedronate were correlated with improvements in BMD and decreases in both Serum Ntx and Alkphase B. There were no relationships between adherence to exercises and changes in BMD or bone turnover (see Table 5).

Table 3 Average measures of lumbar spine, total hip, and femoral neck over time (Time*Group comparisons) (n = 276)

Skeletal sites	Baseline		Six Mos		Twelve Mos		Time*Group interaction
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Lumbar spine (gm/cm^2)							
Control	93	0.889 (0.076)	86	0.887 (0.075)	77	0.885 (0.070)	
Risedronate	91	0.892 (0.06)	82	0.907 (0.066)	78	0.911 (0.070)	RvsE, $p < .010$ RvsC, $p < .001$*
Exercise	92	0.886 (0.064)	82	0.878 (0.062)	72	0.885 (0.065)	
Total n	276		250		227		
Total hip (gm/cm^2)							
Control	92	0.828 (0.067)	85	0.833 (0.070)	76	0.832 (0.069)	
Risedronate	91	0.832 (0.067)	82	0.841 (0.067)	78	0.842 (0.073)	NS differences
Exercise	92	0.848 (0.074)	82	0.855 (0.077)	72	0.858 (0.087)	
Total n	275		249		226		
Femoral neck (gm/cm^2)							
Control	92	0.686 (0.071)	85	0.688 (0.072)	76	0.683 (0.073)	
Risedronate	91	0.696 (0.069)	82	0.700 (0.077)	78	0.701 (0.073)	NS differences
Exercise	92	0.702 (0.073)	82	0.704 (0.072)	72	0.706 (0.079)	
Total n	275		249		226		

Table 4 Average measures of Serum NTx and Alkphase B over time (Time*Group comparisons)

Serum biomarkers	Baseline		Six mos		Twelve mos		Time*Group interaction
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Serum NTx (nmol BCE/L)							
Control	80	13.99 (4.22)	80	12.16 (3.84)	77	12.36 (3.48)	
Risedronate	78	14.31 (4.44)	77	10.30 (3.93)	76	11.42 (4.71)	RvsE, $p < .004$ RvsC, $p < .007$
Exercise	77	15.03 (5.45)	77	13.36 (5.83)	72	13.92 (5.84)	
Total n	235		234		225		
Alkphase B (μg)							
Control	83	13.88 (4.19)	83	12.67 (3.15)	77	12.39 (3.20)	
Risedronate	80	14.47 (4.18)	79	10.92 (3.31)	76	11.13 (3.74)	RvsE, $p < .001$** RvsC, $p < .001$**
Exercise	80	14.61 (5.20)	79	13.51 (4.06)	72	13.69 (4.20)	EvsC, NS
Total n	243		241		225		

Table 5 Correlations between adherence to treatment and 12-month changes in BMD or bone turnover rate in women participating in 12-month testing

Skeletal site or serum biomarker	Correlation between adherence to risedronate and 12-month change in BMD or turnover rate (n = 78)	Correlation between adherence to exercise and 12-month change in BMD or turnover rate (n = 72)
BMD—total spine	$R = 0.49$; $p < .001$	$R = -0.04$; $p = 0.735$
BMD—total hip	$R = 0.29$; $p = .021$	$R = -0.02$; $p = 0.868$
BMD—femoral neck	$R = 0.19$; $p = .130$	$R = -0.057$; $p = 0.634$
Serum Ntx	$R = -0.41$; $p = .001$	$R = -0.03$; $p = 0.793$
Alkphase B	$R = -0.47$; $p < .001$	$R = 0.09$; $p = 0.420$

Discussion

Compared to control and exercise group women, women prescribed risedronate along with CaD had greater improvements in BMD at the spine and greater decreases in rates of bone formation and resorption.

Numerous studies have found BPs to be effective both in increasing BMD and in reducing fracture rate in postmenopausal women [8, 23, 24]. In the Waltman et al. (2010) study, postmenopausal women taking risedronate for 2 years had a 1.81% increase in BMD at the total hip and a 2.85% increase at the spine [23]. Harris et al. (1999) reported that risedronate reduced the incidence of vertebral fractures by 41 to 49% and nonvertebral fractures by 36% over 3 years [8]. In the Siris et al. (2008) study of 620 postmenopausal women with low bone mass, risedronate reduced the risk of fragility fractures by 73% over three years versus use of a placebo ($p = 0.023$) [24].

Although percent increases in BMD have been greater in other studies [23], the sample of women in our study were within their first 6 years of diagnosis of menopause. During early menopause, the average reduction in BMD is 1 to 2% annually [16]. Thus, maintaining BMD and the small increases in BMD in women in our study were positive findings supporting use of BPs.

While there is general agreement that one goal of all treatments for bone loss should be to "at least preserve BMD," Cefalu (2014) suggests that large increases in BMD may not always be related to significant decreases in fractures. In their review of studies on treatment of bone loss, Cefalu reported the amount of change in BMD with treatment correlated poorly with changes in fracture rate [25]. This finding suggests that while low BMD is one cause of fracture, there are multiple other causes.

Four women taking risedronate did report gastrointestinal (GI) symptoms. However, a recent study by Siris et al. (2008) found that when women participated in blinded placebo studies, there was no difference in number of GI symptoms between women who took risedronate and women who took a placebo ($p = 0.78$) [24]. The Siris et al. article did not specifically address incidence of muscle or joint pain with risedronate [24]. Due to eleven women in our study (greater than 10%) reporting incidence in muscle and joint pain with risedronate, providers should be alert for these AEs and monitor patients at follow-up visits. None of the women in our study reported that AEs with risedronate continued after they stopped taking the drug.

BPs have consistently been reported as having relatively acceptable risk–benefit and safety profiles [27]. While women in our study were only prescribed risedronate for twelve months, AEs with long-term use, while extremely rare, have included atypical hip and femur fractures [10].

Researchers have suggested that BPs slow the natural ability of bone to repair the cracks occurring with microdamage over time [9, 10]. Due to concerns about atypical fractures with long-term use, providers frequently discontinue prescriptions for BPs after three to five years in patients who are only a modest risk of fracture [26]. However, even with long-term use, AEs are not likely to outweigh the benefits of BPs. Khosla (2016) and others suggest that articles on atypical fractures have resulted in exaggerated concerns about AEs with BPs. They believe these concerns have resulted in providers not prescribing BPs as often as warranted, and patients refusing to take medications when they are prescribed (27, 28).

In this study, after 12 months, rates of bone resorption and bone formation were significantly reduced in women taking risedronate compared to women in exercise or control groups. For reduction in fracture risk, a goal of treatment should be to reduce serum Ntx levels to at least 12.6 nM BCE or below (the mean value for premenopausal women) [28]. According to Garnero (1996), women with both low hip BMD and high rates of bone resorption have a 4-to-fivefold higher risk of fractures compared to the general population [29, 30].

Biomarkers may be more useful for measuring effectiveness of medications than for exercises. This is because biomarkers reflect changes in overall skeletal bone loss and the whole-body rates of bone resorption and formation. Exercises are targeted to specific skeletal sites, and their effectiveness is better measured by changes in BMD at these specific sites [21].

In our study, after twelve months of bone-loading exercises, women had some improvement in BMD at the spine and total hip, although improvements were greater in the risedronate group. Other studies have reported even greater improvements in BMD with exercise as well as decreases in fracture rates [11–14]. In addition to increasing BMD, exercises have been documented as increasing insulin sensitivity, improving bone structure, balance, gait, and muscle strength, and decreasing risk of falls and depression [31, 32].

Numerous studies of women treated with calcium and vitamin D for bone loss have found greater improvements in BMD over time [33–35]. However, in our study, after 12 months of treatment with calcium and vitamin D supplements, while women in the control group did have increased BMD at the total hip, they had decreases in BMD at the lumbar spine and femoral neck. Compared to the other two treatment groups (risedronate and exercise), women in the control (CaD) group did have less calcium intake at baseline and greater time since menopause (see Table 2). We repeated the hierarchical linear model analyses, this time controlling for calcium sufficiency at baseline and time since menopause in all three treatment groups. No changes in significance

were observed from initial results. Although this does not explain why the control group had greater loss of BMD at 12 months compared to the other two treatment groups, it does rule out the possibility that the observed results can be explained by calcium intake at baseline or time since menopause.

Our findings support the conclusions from a systematic review and meta-analysis by Tai et al. (2015) reporting that prescriptions for calcium and vitamin D alone are unlikely to result in significant increases in BMD and are most useful when they are combined with other therapies, such as BPs and exercises [32]. Although prescribing calcium and vitamin D is better than no treatment, their use alone is unlikely to result in a meaningful reduction in fracture risk [33–35].

In our study, seven women reported that taking calcium supplements caused constipation and other GI symptoms. There have also been reports of renal stones with calcium intake and cardiovascular events with excessive supplements [33]. Because of the potential for adverse events, some experts have recommended that, if possible, elderly women increase their calcium intake through food rather than by taking supplements. Prescriptions for vitamin D supplements were well tolerated by women. Vitamin D supplements have been found to have beneficial effects on muscle performance, balance, and risk of falling as well as bone health [36]. Unfortunately, vitamin D deficiency has been reported as widespread in postmenopausal women and the elderly [38].

Adherence to calcium and vitamin D supplements and risedronate were measured with pill counts. This method has worked well in numerous previous studies of adherence rates, with less than 5% missing pill count data [23]. Adherence to both calcium and vitamin D supplements was optimal—greater than 90%. Mean adherence rates for women participating in exercises were low—58.9%—and no AEs were reported with participation in exercises. Both women and providers fear injuries such as fractures when women with bone loss engage in high-intensity exercises. Our study demonstrated that when women exercise at approved fitness centers, when exercises were monitored by certified ETs, and when weight loads were increased progressively, injuries can be very rare or nonexistent.

Mean adherence to risedronate in this study was 74.9% ± 39.5%, and adherence rates were positively correlated with increases in BMD. There was no relationship between adherence to exercise and changes in BMD. One explanation for this is offered by Beck et al. (2010). According to Beck et al., exercises stimulate bone formation on the outer bone surface (the periosteum). This increase in bone cross-sectional area results in a higher denominator for the calculation of BMD (bone mineral content/region area). Thus, the finding that exercise has minimal or no effect on

BMD may be misleading due to the method for calculating measures of BMD [38].

Finally, the effectiveness of exercises in reducing fracture rate may be underestimated if studies only measure outcomes such as BMD and biomarkers of bone turnover as predictors of fractures. There appear to be multiple causes of fractures in postmenopausal women, and low BMD and high bone turnover are just two of them [38]. In a recent study of 2320 Australian women over the age of 50, Mai et al. (2019) reported that almost 53% of women and 90% of men who sustained a fracture had BMD T-scores > -2.0 [39]. After reviewing findings from numerous studies, Hurley and Armstrong (2012) concluded that both BPs and exercises could improve bone strength and reduce fracture risk. However, they worked through different mechanisms. BPs improved bone strength by increasing BMD at the spine, hip, and femoral neck and by reducing the rate of bone loss. Bone-loading exercises were more likely to strengthen bones and reduce fractures by maintaining BMD, improving bone structure, muscle strength, balance, and gait and by reducing falls [41].

Limitations

The optimal goal of enrolling 302 participants in the study was not met. Another limitation is that 49 of the 276 participants enrolled withdrew during the study, or greater than 17%. Also, a greater number of women in the exercise group ($n = 20$) withdrew, compared to women in the control ($n = 16$) or risedronate group ($n = 13$). Finally, because of the homogenous nature of our sample population (average age of 54 years, majority were white/non-Hispanic and highly educated, all women were from one Midwestern state), results cannot be generalized to other populations of women. Less than 15% of the sample of 276 women enrolled were from minority populations. The underrepresentation of Hispanic and Asian women in osteoporotic studies is especially a concern because these women are considered at increased risk for bone loss and osteoporosis [41].

Future directions

The primary aim of treatment for postmenopausal women with bone loss is to reduce incidence of fractures. A future study for our research team would be to examine whether BMD and bone turnover changes after 12 months of treatment translated into decreased fracture rates. Future studies should be conducted examining risk factors for fractures in postmenopausal and elderly women in addition to low BMD and increased rate of bone turnover. Individual programs

could be developed for women that would include prescribing interventions for prevention of fractures most applicable to each of the women's assessed needs.

Conclusions

Conclusions from our study are that postmenopausal women with low bone mass should be encouraged to obtain adequate calcium and vitamin D and participate in bone-loading exercises. Also, the additional use of BPs will increase BMD, especially at the spine. Decision-making as to whether individual women with low bone mass should be prescribed BPs should be determined by assessments of these women that could include measures of BMD, bone turnover, bone structure, FRAX scores, and other risk factors for fractures including a sedentary lifestyle; concerns about adverse effects of BPs with both short-term and long-term use; and incorporating patient preferences into treatment. Women will be more likely to adhere to their medication and treatment regimen if they have had input into their plan of care [42].

Abbreviations BMD: Bone mineral density; BPs: Bisphosphonates; CaD: Calcium and vitamin D supplements; CORC: Creighton University Osteoporosis Research Center; DXA: Dual-energy X-ray absorptiometry; ETs: Exercise trainers; FRAX: Fracture risk assessment; GI: Gastrointestinal; HSA: Hip structural assessment; Lbs.: Pounds; LIFTMOR: Lifting Intervention for Training Muscle and Osteoporosis Rehabilitation; NOF: National Osteoporosis Foundation; pQCT: Peripheral quantitative computed tomography; 1RM: One-repetition maximum

Author contribution All authors were involved in the implementation of this R01-funded study. All authors read and approved this final manuscript. Dr. Waltman[1] developed the research project, wrote the initial draft of the manuscript, and assisted in analyzing and interpreting results of the study. Dr. Kevin Kupzyk[2] was a co-investigator in the study, conducted the power analysis to determine sample size for the study, assisted in data analysis for this study, and reviewed and critiqued the final writing of this manuscript. Laura Flores[3] provided valuable information on bone mineral density and bone structure during the analysis of study results and reviewed and critiqued the drafts of the manuscript. Dr. Lynn Mack[4] and Dr. Joan Lappe[5] were co-investigators for the study and assisted in designing and implementing the study. They reviewed and critiqued the final writing of this manuscript. Dr. Laura Bilek[6] was co-principal investigator for the study. In addition to development of this research project, she participated in and supervised recruitment of subjects, data collection, and data entry for the study. She reviewed and critiqued the statistical analysis and the final writing for this manuscript.

Declarations

Conflicts of interest None.

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