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The independent and combined effects of intensive weight loss and exercise training on bone mineral density in overweight and obese, older adults with osteoarthritis

Daniel P. Beavers, PhD¹, Kristen M. Beavers, PhD², Richard F. Loeser, MD³, Nicole R. Walton, DO³, Mary F. Lyles, MD², Barbara J. Nicklas, PhD², Sue A. Shapses, PhD⁴, Jovita J. Newman, MA⁵, and Stephen P. Messier, PhD⁵

¹Department of Biostatistical Sciences (dbeavers@wakehealth.edu)

²Section on Gerontology and Geriatric Medicine (kbeavers@wakehealth.edu, bnicklas@wakehealth.edu, mlyles@wakehealth.edu)

³Section on Molecular Medicine (rloeser@wakehealth.edu, dr.nwalton@gmail.com), Wake Forest School of Medicine, Winston-Salem, NC

⁴Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ (shapses@aesop.rutgers.edu).

⁵Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC (jollajk@wfu.edu, messier@wfu.edu)

Abstract

Objective—To determine the effects of dietary-induced weight loss (D) and weight loss plus exercise (D+E) compared to exercise alone (E) on bone mineral density (BMD) in older adults with knee osteoarthritis (OA).

Design—Data come from 284 older (66.0±6.2 years), overweight/obese (BMI 33.4±3.7 kg/m²), adults with knee OA enrolled in the Intensive Diet and Exercise for Arthritis (IDEA) study. Participants were randomized to 18 months of walking and strength training (E; n=95), dietary-induced weight loss targeting 10% of baseline weight (D; n=88) or a combination of the two (D

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Corresponding author: Daniel P. Beavers, PhD Wake Forest School of Medicine Winston-Salem, NC 27157 Phone: 336-713-1616 dbeavers@wakehealth.edu.

Author Contributions The authors' responsibilities were as follows—SPM, BJN and RFL: designed the research; JJN, RFL, MFL, BJN, NRW and SPM: conducted the research; DPB and KMB: analyzed the data; DBP, KMB, RFL, NW, MFL, BJN, and SAS: interpreted the data and drafted the manuscript; and DPB: had primary responsibility for the final content. All authors read and approved the final manuscript.

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+E; n=101). Body weight and composition (DXA), regional BMD, were obtained at baseline and 18 months.

Results—E, D, and D+E groups lost 1.3±4.5 kg, 9.1±8.6 kg and 10.4±8.0 kg, respectively ($p<0.01$). Significant treatment effects were observed for BMD in both hip and femoral neck regions, with the D and D+E groups showing similar relative losses compared to E (both $p<0.01$). Despite reduced BMD, fewer overall participants had T-scores indicative of osteoporosis after intervention (9 at 18 months vs. 10 at baseline). Within the D and D+E groups, changes in hip and femoral neck, but not spine, BMD correlated positively with changes in body weight ($r=0.21$ and 0.54 respectively, both $p<0.01$).

Conclusions—Weight loss via an intensive dietary intervention, with or without exercise, results in bone loss at the hip and femoral neck in overweight and obese, older adults with OA. Although the exercise intervention did not attenuate weight loss associated reductions in BMD, classification of osteoporosis and osteopenia remained unchanged.

Keywords

bone density; obesity; weight loss; exercise; osteoarthritis

Introduction

Osteoarthritis (OA) is a leading cause of disability in older adults¹, with obesity recognized as the strongest modifiable risk factor for the condition. Even modest weight loss (i.e. 5% of baseline weight) substantially improves physical function in this population^{2, 3}. Nonetheless, concern exists about weight loss-associated reductions in lean and bone mass^{4, 5}, and the potential for exacerbation of age-related risk of disability^{6, 7} and osteoporotic fracture^{8, 9}. Regarding the latter, although patients with obesity and OA typically present with high bone mineral density (BMD)¹⁰, paradoxically, they may be at increased risk of fracture¹¹⁻¹³. Sustained fractures, especially at the hip, compromise quality and expectancy of life^{14, 15}; thus, identification of adjuvants to weight loss that minimize bone loss in obese, older adults with OA is warranted¹⁶.

Numerous strategies have been proposed to reduce bone loss during weight loss, including behavioral interventions. Several studies show a positive effect of exercise training on BMD in weight stable, older adults^{17, 18}, and it may be an effective means to prevent bone loss during weight loss. Some, but not all¹⁹⁻²¹, studies show that performing regular weight-bearing (e.g., walking) and/or muscular loading (e.g., resistance) exercise may preserve bone during weight loss²²⁻²⁵. Results of these studies, however, are highly variable and may not be generalizable to older adults with chronic conditions that limit exercise capacity, such as OA.

Whether exercise can prevent weight loss-associated bone loss in older, obese adults with OA is not yet known. Therefore, the primary purpose of this study is to begin to determine the effects of dietary-induced weight loss plus walking and strength training exercise (D+E) compared to dietary-induced weight loss (D) and exercise (E) alone on regional BMD and T-scores at the hip and spine in a subset of overweight and obese, older adults with OA

participating in the Intensive Diet and Exercise for Arthritist (IDEA) study. Secondly, we describe the relationships between change in BMD and change in body weight, composition, and adiposity in the treatment arms undergoing intentional weight loss (D+E and D).

Methods

Study design and participants

Participants included in the present analysis were enrolled in the IDEA study, a single-blinded, randomized, controlled trial (RCT) designed to determine whether significant weight loss (i.e. 10% reduction in body weight induced by diet, with or without exercise) improves mechanistic (knee joint loads and inflammation) and clinical (pain, function, mobility, and health-related quality of life) outcomes more than exercise alone in overweight and obese, older adults with knee OA^{3, 26}. A total of 454 participants were originally randomized (using a computer based permuted random block design, within BMI and gender subgroups) to 18-months of E, D, or D+E, a subset of which consented to baseline, DXA-acquired, areal BMD measurement of the hip and lumbar spine (n=129, 128 and 135 for E, D, and D+E groups at baseline, respectively). All participants were offered DXA scans, but participants were allowed to refuse due to concerns about radiation exposure or schedule conflicts. Participants were lost to follow up during the trial due to study attrition (n=108), and missing data are assumed missing at random. The present analysis utilizes only the participants in whom we obtained a baseline and 18-month DXA scan (n=284, see Figure 1).

Individuals were eligible to participate in the IDEA study if they were ambulatory, community-dwelling, sedentary (< 30 minutes/week of formal exercise within the past six months), overweight or obese (27.0 < body mass index (BMI) < 40.1 kg/m²), older (> 55 years) adults who had grade II-III (mild to moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees. The Wake Forest University institutional review board approved the study, all participants signed an informed consent, and the primary outcome paper has been published³.

Interventions

Intensive dietary induced weight loss intervention—Both the D and D+E groups received the same dietary intervention, with an average weight loss goal of 10-15% of baseline weight. The dietary plan was based on partial meal replacements, including up to two meal-replacement shakes per day (General Nutrition Centers, Inc., Pittsburgh, PA.), with each shake providing 500 mg of calcium. For the third meal, participants followed a weekly menu plan and recipes that were low in fat, and high in vegetables, and provided 500-750 kcals/day. Collectively, the diet plan provided an energy-intake deficit of 800–1000 kcals/day, as predicted by resting energy expenditure (estimated resting metabolism × 1.2 activity factor), with 15–20% of calories coming from protein, < 30% from fat, and 45–60% from carbohydrate.

Body weight was monitored in weekly nutrition and behavior education sessions. Individuals trained in behavioral therapy and experienced in working with older adults ran

all group and individual sessions, with one individual session and three group sessions per month for the first six months. Behavioral session topics included problem solving, goal-setting, review of a specific food topic, and tasting of several well balanced, low-fat, nutritious foods prepared with easily available ingredients. From months seven to 18, participants attended biweekly group behavioral sessions, with an individual appointment every two months.

Exercise Intervention—The D+E and E groups received the same exercise intervention, which consisted of overground walking (15 minutes), strength training (20 minutes), a second walking phase (15 minutes), and cool-down (10 minutes) three days per week for 18 months. During the first six months, participation was center-based. After the initial six-months, participants could remain in the facility program, opt for a home-based program, or combine the two. Further details of the interventions used in all treatment arms can be found in the IDEA design and rationale paper²⁶.

Body Composition and Clinical Classification of BMD

All outcome measures were assessed by blinded study staff. Participant height and body mass were assessed at baseline and 18 months. Height was measured using a stadiometer and body mass was measured on a calibrated electronic scale. BMI was calculated as body mass in kg divided by height in meters squared. Total body fat and lean mass, and regional BMD were assessed using dual-energy X-ray absorptiometry (DXA, Hologic Delphi A 11.0 QDR, Bedford, MA) at baseline and 18 months. Specifically, bone density (BMD; g/cm²) was measured at the posterior anterior lumbar spine (L1-L4) and hip (femoral neck, trochanter, and intertrochanter space). DXA measurements were made by a certified technician blinded to treatment arm and the manufacturer's recommendations for patient positioning, scanning, and analysis scans were followed. Osteoporosis and osteopenia were defined as location-specific T-scores ≤ -2.5 and between -2.5 and -1 , respectively²⁷.

Covariate Measurements

Baseline covariate assessments included self-reported demographic, medical history, and comorbidity information. Prescription bone medication usage and calcium/vitamin D supplementation were also captured via self-report at baseline.

Serum Leptin

Serum leptin concentration was measured as a biomarker of adiposity and a potential mediator of the adiposity-BMD association²⁸. Blood draws were performed on a subsample of participants (n=116) in the fasted state at baseline and 18-months and tested using a commercial radioimmunoassay (Millipore, Billerica, MA). The subsample consisted of participants that consented to additional MRI and CT scans, who were selected as a random sample from the latter waves of study recruitment.

Statistical Analysis

Descriptive statistics were summarized by intervention group at baseline using means \pm standard deviations or frequencies and percentages. The overall intervention effect on

change in regional BMD was estimated using one-way ANOVA (unadjusted results) and analysis of covariance (ANCOVA, adjusted results), with results presented as means and 95% confidence intervals. The ANCOVA model testing the intervention effect included adjustment for gender, baseline BMI and baseline regional BMD value in accordance with the IDEA trial analytic plan²⁶ to accommodate study stratification factors and to ensure that the variance is not biased. To ensure findings were not affected by bone medication and supplement use, additional ANCOVA models (as previously described) were performed, further adjusting for prescription bone medication use or calcium/vitamin D supplementation.

Associations between intentional weight (and body composition) loss and change in BMD from baseline were assessed in D and D+E arms, only. Pearson correlations were generated to measure the strength of the association between percentage changes in body weight and changes in regional BMD. Eighteen month change in regional BMD per kg change in body mass and composition or per ng/dL change in leptin was modeled using linear regression, adjusting for randomization arm, gender, baseline BMI, and baseline outcome measure. Because leptin is often considered a global adiposity biomarker, the previous association between leptin and percent BMD change was further adjusted for change in total fat mass. Lastly, to aid in clinical interpretability and detect a potential nonlinear associations between BMD and weight change, associations between change in regional BMD by overall percent weight change were modeled using ANCOVA with percent weight change tertile as the independent variable, adjusted for randomization arm, gender, baseline BMI, and baseline regional BMD.

SAS software (version 9.3, SAS Institute Inc, Cary, NC) was used for all analyses, with a Type I error rate of 0.05 for overall group comparisons and associations. Pairwise comparisons of treatment arms were deemed significant at a Bonferroni-adjusted Type I error rate of 0.0167, as prescribed in the IDEA analytic plan²⁶.

Results

Baseline characteristics

Recruitment and retention characteristics of the present analysis are presented in Figure 1. Baseline DXA measurements were performed on 392 of the 454 IDEA trial participants, and 284 participants who had a baseline DXA scan returned for an 18-month visit scan. Race was the only significant predictor of DXA study attrition, with African-American participants more likely to withdraw (41.2%) than white participants (26.5%, $p=0.02$). Baseline demographic data on the IDEA study sample used in this analysis ($n=284$) are presented by treatment arm in Table 1. Overall, participants were 66.0 ± 6.2 years of age with an average BMI of 33.4 ± 3.7 kg/m². Women represented 74% of the study sample and 86% self-identified as Caucasian, similar to the total IDEA sample³. Although only 9% of participants self-reported a prior diagnosis of osteoporosis, reported use of bone prescription medication was 25%, and reported use of calcium and vitamin D supplementation was 51%. Based on DXA-acquired BMD and calculated T-scores, 179 (47%) participants were classified as osteopenic and 15 (4%) participants were classified as osteoporotic at baseline.

Intervention effect on BMD and clinical classification

Over the 18-month intervention period an average of 9.1 ± 8.6 kg ($9.7\pm 8.5\%$) and 10.4 ± 8.0 kg ($11.3\pm 8.3\%$) of initial body weight was lost in the D and D+E arms, respectively (both $p<0.01$), with a minimal but significant loss in body weight observed in the E-only group (1.3 ± 4.5 kg, $1.4\pm 4.6\%$; $p<0.01$). Mean diet session attendance for D ($67.8\pm 17.8\%$) and D+E groups ($68.7\pm 19.7\%$) did not significantly differ ($p=0.75$); likewise, mean exercise session attendance did not differ by group (E = $61.1\pm 21.6\%$ and D+E= 63.2 ± 20.9 ; $p=0.49$).

Unadjusted and adjusted 18-month treatment effects on BMD are presented in Table 2. Significant treatment effects were observed for both hip and femoral neck regions, with the D and D+E groups showing significant absolute and relative losses in BMD compared to E. Although 18-month hip and femoral neck BMD measurements did not significantly differ from baseline in the E-only group, it is worth noting that estimates were negative. Results were largely unchanged after adjustment for gender, baseline BMI, and baseline regional BMD value. No treatment effect was observed for spine BMD. Further analyses adjusting for baseline prescription bone medication use or calcium/vitamin D supplementation did not modify the observed treatment effects (data not shown).

Ten participants with baseline and follow-up DXA-derived T-score values were classified as osteoporotic (1 hip, 3 femoral neck and 6 spine) and 46.8% (133) had osteopenia in at least one site at baseline. Following intervention, nine participants had T-scores indicative of osteoporosis in any region and 49.3% (140) had osteopenia. Only one participant (D group) progressed from osteopenia to osteoporosis while two participants (one E and one D) classified as osteoporotic at baseline changed to osteopenia at 18 months. Eleven participants (2 E, 3 D, 6 D+E) progressed from normal BMD to osteopenia in at least one region at 18 months.

Associations between measures of body weight, composition, and adiposity and regional BMD change

To assess the independent contribution of the magnitude of intentional weight loss on change in percent BMD, the E-only group was removed from the following analyses, and D and D+E group were combined (see Table 3). For D and D+E groups, changes in femoral neck and hip BMD correlated positively with changes in body weight ($r=0.21$ and 0.54 , both $p<0.01$). Model-adjusted estimates controlling for randomization group, gender, baseline BMI, and baseline outcome measures revealed a 1 kg loss in body weight was associated with a $0.10\pm 0.03\%$ reduction in femoral neck BMD and a $0.20\pm 0.03\%$ reduction in hip BMD. While changes in both fat mass and lean mass were significantly associated with percent change in hip BMD, only fat mass changes were associated with change in femoral neck BMD.

The relationship between change in bone density and body weight and composition was also modeled by comparing change in regional BMD by tertile of percentage weight loss for the D and D+E groups only (Table 4, no interaction was found between randomization group and tertile of weight loss). Participants experiencing the greatest weight loss (12.9%) showed markedly greater reductions of BMD at the femoral neck and hip, but not the spine,

compared to participants in the lowest tertile of weight loss (<5.2%). Similar results were observed when losses of fat and lean mass were considered (data not shown).

Lastly, as a potential mediator of the association between change in fat and bone mass, associations between change in regional bone mass and change in serum leptin were assessed. Unadjusted associations, shown in Figures 2a-2c, suggest a direct relationship, with a stronger linear association between change in leptin and change in hip BMD ($r=0.43$, $p<0.01$) and between leptin change and femoral neck change ($r=0.41$, $p<0.01$) when compared to spine BMD change and leptin change ($r=0.10$, $p=0.09$). Model-adjusted change in leptin was significantly associated with change in BMD for each location, although all associations became nonsignificant after further adjustment for total body fat mass (see Table 3).

Discussion

Results from this exploratory study provide novel information about the independent and combined effects of intensive dietary-induced weight loss and exercise training on regional BMD in overweight and obese, older adults with knee OA. We report that 10% weight loss occurring over 18-months, with or without exercise, is associated with significant reductions in hip and femoral neck, but not spine, BMD. Participants who lost the most weight and fat mass also lost the most hip and femoral neck BMD, regardless of baseline BMI, BMD, or exercise status. However, despite significant BMD loss, clinical classification of osteoporosis and osteopenia remained virtually unchanged.

The addition of exercise to dietary-induced weight loss is hypothesized to attenuate the loss of BMD associated with weight loss by countering reductions in mechanical stress²⁹. Indeed, exercise in the absence of weight loss is consistently shown to have a positive effect on BMD in older adults^{17, 18}. To date, however, only four RCTs (including the present study) have been designed to examine the additive effect of exercise training to dietary-induced weight loss on BMD in older adults, with conflicting results reported. The first study, conducted in 1993 by Svendsen and colleagues¹⁹, enrolled 118 overweight postmenopausal women to participate in a 3-arm (control, diet, and diet plus combined aerobic/non-aerobic exercise) 12-week RCT. Despite significant weight loss achieved in the diet groups compared to control, no consistent, major group differences in total body, spinal, or forearm BMD were observed¹⁹. These seminal findings suggest that the addition of exercise to weight loss does not prevent bone loss, although the short duration of this study intervention likely compromised the ability to observe significant changes in bone remodeling between treatment arms³⁰. In contrast, two recent, longer RCTs suggest that exercise (high intensity resistance training²³ or a combined aerobic and resistance training program²⁵) is effective for maintaining total body²³ and regional²⁵ bone mass in overweight and obese older adults undergoing intentional weight loss.

The study design and outcomes assessed by Shah et al.²⁵ most closely resemble the current study and, given discordant results, it is of interest to speculate which study characteristics contributed to the conflicting findings. Although total weight loss achieved in diet groups and exercise modality/frequency were similar between the studies, differences were noted in

exercise duration (90 minutes/day²⁵ versus 60 minutes/day in the present study) and adherence (83%²⁵ versus 63% in our study, in combined diet and exercise groups). Importantly, and in contrast to our findings, the exercise intervention utilized by Shah et al.²⁵ increased hip BMD in the exercise-only group over time, suggesting that increased compliance to exercise prescriptions of longer duration may significantly influence change in BMD. That being said, the time course of the two studies was different (12 months²⁵ versus 18 months in our study), and a true cross-study comparison requires consideration of normal age-related bone loss (i.e. ~ 1% per year)³¹⁻³³. Thus, participants in the IDEA study would have been expected to lose greater amounts of BMD simply due to the longer duration of the study, which may or may not be mitigated by exercise training. Finally, although both studies sampled overweight and obese, older adults with functional limitations (mild-to-moderate frailty²⁵ versus OA in the present study), persons with OA have unique risks for fracture^{11, 12} and compromised exercise ability³⁴, which require separate characterization. Findings from Shah et al²⁵ and other RCTs of exercise may not be applicable to this population, as the total exercise dose realistically achievable by persons with OA may not be sufficient to prevent age- and weight loss-associated BMD loss.

Findings presented here examining the magnitude of BMD loss associated with weight loss are in line with other weight loss trials reporting a 1-2% reduction in regional BMD associated with a 10% loss in baseline weight⁵. Results also concur with prior literature in older adults showing that when diet and exercise groups are compared to a weight stable group, weight loss is consistently associated with reduced BMD^{19, 21, 25} and that changes in fat mass are directly correlated to changes in bone mass^{35, 36}. Leptin data presented here lend support to the hypothesis that weight loss-induced reductions in leptin could belie the association between weight loss and bone loss²⁸; however, it is worth noting that this relationship did not hold after further adjustment for fat mass change, which has been shown before³⁷.

Clinically, weight loss-associated loss in BMD is concerning due to the well-known association between low BMD and fracture risk^{9, 38}. Indeed, BMD is the strongest predictor of future osteoporotic fracture,³⁹ and observational data consistently link weight loss in late life with loss of BMD^{8, 9}; yet, whether the magnitude of BMD loss observed in this study translates into increased fracture risk remains unknown. Encouragingly, clinical classification of osteoporosis and osteopenia was unchanged in IDEA participants undergoing weight loss. Moreover, although the exercise prescription utilized in IDEA did not prevent reductions in BMD, fracture risk assessment is multifactorial and overall risk may be reduced due to parallel improvements in pain and function attributable to the study intervention³.

Strengths of the present study include the RCT design, large sample size and serial measures of BMD at clinically important sites of osteoporotic fracture. This study is not without limitations, however. First, the main IDEA trial was conceived and executed to explore the effect of E, D, and D+E on IL-6 and knee compressive forces²⁶; thus, the present analysis is an exploratory investigation of the effect of body composition changes on BMD within a random subgroup of the IDEA trial. Because this specific analytic plan and study power were not determined *a priori* at the time of the trial's inception, findings should be

considered hypothesis-generating rather than confirmatory. Second, although DXA-acquired areal BMD is the primary metric by which osteoporosis is assessed, it is insufficient to quantify future fracture risk⁴⁰, and presents a number of methodological limitations in the context of obesity and weight loss^{41;42}. Future studies evaluating intervention effectiveness on skeletal health would be strengthened by the integration of measures of bone quality⁴³, such as volumetric BMD, thickness and strength estimates, which should improve fracture risk predictive power. Third, the age and proclivity of our study population to develop osteophytes⁴⁴ may have influenced BMD measures, and results may not be generalizable to older adults without OA. Additionally, the possibility that overweight and obese adults develop leptin resistance raise questions about whether our sample is appropriate for studying any leptin-bone association⁴⁵. Lastly, the protective effect of calcium supplementation⁵ osteoporosis medications on BMD during weight loss is strong⁴⁶ and, although statistical adjustment for calcium/vitamin D intake or medication use did not affect study results, the protective effect of pharmacotherapy on BMD may have compromised our ability to observe lifestyle-based differences.

In summary, 18-months of intensive dietary induced weight loss, with or without exercise training, in overweight and obese older adults with OA results in bone loss at the hip and proximal femur. Although the exercise intervention did not attenuate weight loss-associated reductions in BMD, clinical classification of osteoporosis and osteopenia in the population remained unchanged. Future intervention studies seeking to evaluate and minimize the risk/benefit ratio associated with weight loss in overweight and obese older adults need to include osteoporosis-related fractures as an endpoint. Further, additional clarification as to the duration, intensity, and type of exercise necessary to minimize bone loss in older adults undergoing intentional weight loss – including those with disease specific conditions, such as OA, that are often ignored - is needed from well-designed RCTs.

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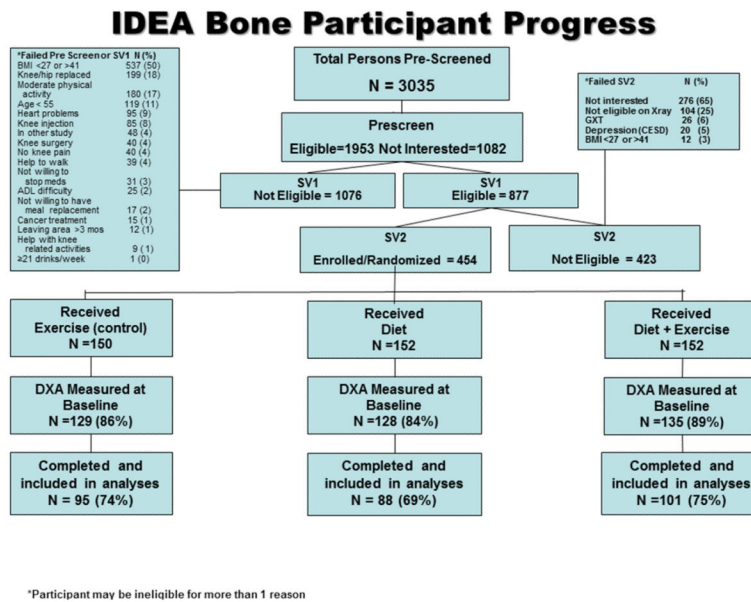


Figure 1.
IDEA Bone Consort Diagram

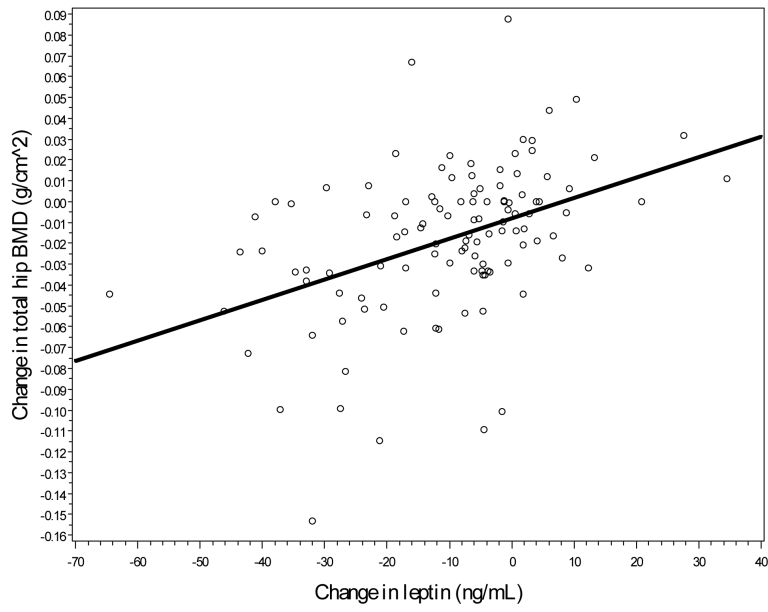


Figure 2a.
Linear association between hip BMD changes and leptin changes

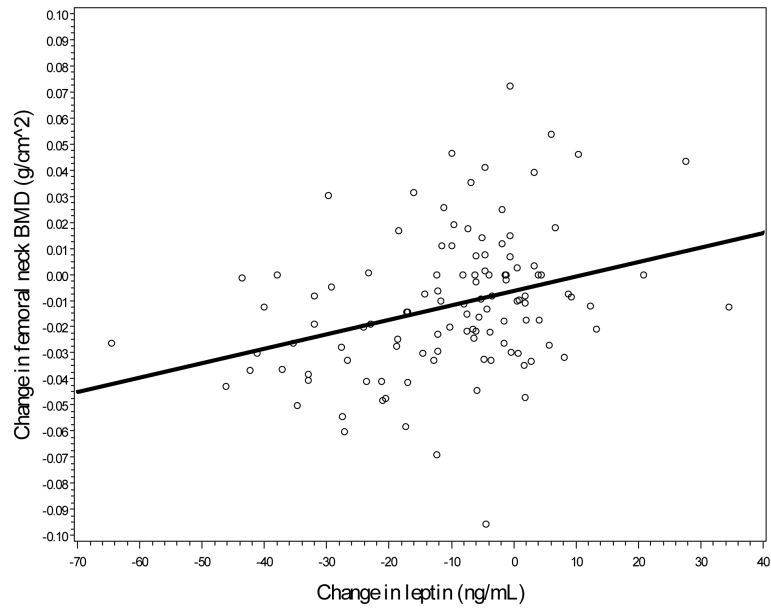


Figure 2b.
Linear association between femoral neck BMD changes and leptin changes.

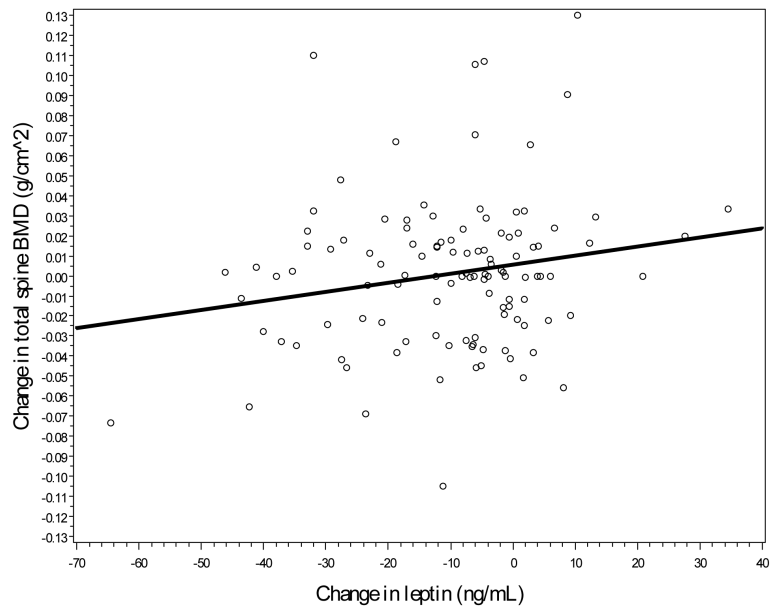


Figure 2c.
Linear association between spine BMD changes and leptin changes.

Table 1

Baseline descriptive characteristics according to treatment group for individuals with baseline and follow-up DXA data.

Participant Characteristics	Exercise (n=95)	Diet (n=88)	Diet + Exercise (n=101)
Age (years)	65.8±6.3	66.0±6.0	66.1±6.4
Female, n (%)	71 (75)	61 (70)	77 (76)
White, n (%)	80 (84)	79 (90)	85 (84)
Weight (kg)	91.6±13.5	91.8±15.0	91.4±14.1
Body mass index (kg/m ²)	33.5±3.7	33.2±3.6	33.4±3.7
Total body fat mass (kg)	36.6±7.9	36.5±7.1	36.3±8.5
Total body lean mass (kg)	55.5±11.5	55.1±12.4	54.6±10.9
Leptin (ng/mL) [*]	40.8±20.5	36.6±22.4	37.8±28.5
Self-reported osteoporosis	6 (6)	9 (11)	9 (9)
Self-reported bone medication use ^{**}	24 (25)	18 (20)	28 (28)
Self-reported calcium/vitamin D use	55 (58)	40 (45)	49 (49)
Areal bone mineral density (BMD)			
Hip BMD (mg/cm ²)	968±135	981±162	962±120
Femoral neck BMD (mg/cm ²)	792±109	805±124	791±109
Spine BMD (mg/cm ²)	1070±176	1080±199	1070±161
T-score			
Hip	0.02±0.95	0.05±1.11	-0.02±0.88
Femoral neck	-0.66±0.88	-0.59±1.00	-0.66±0.91
Spine	0.13±1.54	0.17±1.71	0.10±1.39
DXA-derived osteoporosis ^{***} , n (%)	2 (2)	5 (6)	3 (3)
DXA-derived osteopenia ^{***} , n (%)	50 (53)	44 (44)	39 (44)

Data are presented as means ± SD or n (%). Abbreviations: n = sample size; kg = kilogram; m = meter; g = gram; cm = centimeter; DXA = dual energy x-ray absorptiometry.

* Leptin total subsample with BL and 18-month measures: n=116 (E: n=39; D: n=36; D+E: n=41).

** Queried bone medications include Actonel, Fosamax, Boniva, and Forteo.

*** Baseline osteoporosis and osteopenia classifications were based on a DXA-acquired BMD T-score -2.5 or $-2.5 < \text{T-score} < -1$ at the hip, femoral neck or spine, respectively.

Table 2

Unadjusted and adjusted treatment effects on change in BMD by region.

Change in BMD by Region	Exercise (n=95)			Diet (n=88)			Diet + Exercise (n=101)			Overall p-value*
	Mean (95% CI)	% Chg	Mean (95% CI)	% Chg	Mean (95% CI)	% Chg	Mean (95% CI)	% Chg		
Total Hip BMD (mg/cm ²)										
Unadjusted	-2.1 (-8.2, 4.0)	-0.2	-24.0 (-30.3, -17.6)	-2.5	-19.4 (-25.3, -13.5)	-2.0			<0.01**	
Adjusted	-2.0 (-8.5, 4.4)	-0.2	-23.7 (-30.3, -17.2)	-2.4	-19.5 (-25.8, 13.2)	-2.0			<0.01**	
Femoral Neck BMD (mg/cm ²)										
Unadjusted	-2.6 (-8.2, 2.9)	-0.3	-15.3 (-21.0, -9.5)	-1.9	-14.4 (-19.8, -9.1)	-1.8			<0.01**	
Adjusted	-0.8 (-6.6, 5.0)	-0.1	-13.2 (-19.1, -7.3)	-1.7	-12.5 (-18.1, -6.8)	-1.6			<0.01**	
Spine BMD (mg/cm ²)										
Unadjusted	5.2 (-2.1, 12.4)	0.5	3.5 (-4.0, 11.0)	0.3	-0.9 (-7.9, 6.1)	-0.1			0.47	
Adjusted	7.5 (-0.2, 15.1)	0.7	5.4 (-2.4, 13.2)	0.5	1.5 (-6.0, 9.0)	0.1			0.50	

Unadjusted estimates are based on a one-way ANOVA at 18 months. Model-adjusted estimates control for gender, baseline BMI and baseline risk factor value. Abbreviations: BMD = areal bone mineral density; n = sample size; SE = standard error.

* p-value at 18 months performed based on test from a contrast statement to compare groups.

** E differs significantly from D and D+E (p<0.01)

Table 3

18-month changes in BMD from baseline per unit change in measures of body composition and leptin, D and D+E arms only.

Change in Body Weight and Composition	Total Hip BMD (mg/cm ²)		Femoral Neck BMD (mg/cm ²)		Spine BMD (mg/cm ²)	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Total body weight (kg)	1.9 (1.5, 2.4)	<0.01	0.8 (0.3, 1.3)	<0.01	0.4 (-0.3, 1.01)	0.19
Total body lean mass (kg)	3.8 (2.3, 5.4)	<0.01	1.4 (-0.0, 2.8)	0.06	-0.00 (-1.8, 1.8)	0.99
Total body fat mass (kg)	2.8 (2.1, 3.4)	<0.01	1.2 (0.5, 1.8)	<0.01	0.8 (-0.0, 1.66)	0.06
Leptin (ng/dL)*	1.2 (0.7, 1.7)	<0.01	0.7 (0.3, 1.0)	<0.01	0.6 (0.0, 1.1)	0.04
Leptin (ng/dL), further adjusted for fat mass change**	0.3 (-0.2, 0.8)	0.26	0.4 (0.0, 0.8)	0.05	0.5 (-0.2, 1.2)	0.14
Leptin (ng/dL), further adjusted for fat mass change**	0.3 (-0.2, 0.8)	0.26	0.4 (0.0, 0.8)	0.05	0.5 (-0.2, 1.2)	0.14

Model estimates adjust for randomization group, gender, baseline BMI, and baseline location BMD value.

* Statistical significance ($p < 0.05$) unchanged using log-leptin in model in place of leptin except for spine (log-leptin $p = 0.16$).

** Nonsignificance ($p > 0.05$) unchanged using log-leptin in place of leptin.

Table 4

Change in bone mineral density by tertile* of percentage weight loss, D and D+E arms only.

Change in BMD by Region	Tertile 1 (n=72)	Tertile 2 (n=73)	Tertile 3 (n=72)	Overall <i>p</i> -value*
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Total Hip BMD (mg/cm ²)	-5.0 (-12.9, 2.9)	-18.5 (-25.8, -11.2)	-36.6 (-43.7, -29.5)	<0.01
Femoral Neck BMD (mg/cm ²)	-6.2 (-13.7, 1.3)	-8.0 (-14.9, -1.1)	-21.5 (-28.2, -14.8)	<0.01
Spine BMD (mg/cm ²)	10.1 (-4.0, 21.1)	6.8 (-5.7, 19.3)	-1.7 (-13.6, 10.2)	0.37

* Where Tertile 1 experienced <5.18% weight loss, Tertile 2 experienced 5.18% but <12.86% weight loss and Tertile 3 experienced 12.86% weight loss.

All tertiles for total hip achieve pairwise statistical significance ($p < 0.0167$). Additionally, tertile 3 compared to tertiles 1 and 2 for femoral neck achieves pairwise significance.

Model estimates adjusted for randomization arm, gender, baseline BMI, and baseline regional BMD.