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Effect of weight loss on bone health in overweight/obese postmenopausal breast cancer survivors

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Abstract

Purpose—Current guidelines recommend weight loss in obese cancer survivors. Weight loss, however, has adverse effects on bone health in obese individuals without cancer but this has not been evaluated in breast cancer survivors. We investigated the associations of intentional weight loss with bone mineral density (BMD) and bone turn over markers in overweight/obese postmenopausal breast cancer survivors.

Methods—Participants were overweight/obese breast cancer survivors (N=81) with stage I, II or IIIA disease enrolled in the St. Louis site of a multi-site Exercise and Nutrition to Enhance Recovery and Good health for You (ENERGY) study; a randomized controlled clinical trial designed to achieve a sustained ≥7% loss in body weight at 2 years. Weight loss was achieved through dietary modification with the addition of physical activity. Generalized estimating equations were used to assess differences in mean values between follow-up and baseline.

Results—Mean weight decreased by 3% and 2.3% between baseline and 6-month follow-up, and 12-month follow-up, respectively. There were decreases in osteocalcin (10.6%, p-value<0.001), PINP (14.5%, p-value<0.001), NTx (19.2% p-value<0.001), and RANK (48.5%, p-value<0.001), but not BALP and CTX-1 levels between baseline and 12-month follow-up. No significant changes occurred in mean T-scores, pelvis and lumbar spine BMD between baseline and 12-month follow-up.

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Conflict of interests

The authors declare that they have no conflict of interest

Conclusion—A 2.3% weight loss over 12 months among overweight/obese women with early stage breast cancer does not appear to have deleterious effect on bone health, and might even have beneficial effect. These findings warrant confirmation, particularly among breast cancer survivors with a larger magnitude of weight loss.

Keywords

breast cancer; bone health; obesity; weight loss; bone mineral density

Introduction

There are > 3.1 million breast cancer survivors in the United States, 90% of who are aged ≥50 years [5]. With improving survival, this number will continue to increase. Thus, a good understanding of factors that impact health outcomes, including bone health, in postmenopausal breast cancer survivors is essential. Further, most pre-menopausal breast cancer survivors become post-menopausal with chemotherapy, with associated accelerated bone loss [3]. It is estimated that >40% of postmenopausal women will have at least one osteoporotic fracture, which could lead to disability [27]. In addition to bone loss arising from the low estrogenic state of menopause, secondary bone loss resulting from cancer treatment is a major concern among postmenopausal women with breast cancer. Chemotherapy and treatment with aromatase inhibitors (AI) are associated with increased risk of osteoporosis and fracture [6]. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, 5-year treatment with anastrazole was associated with clinically significant decreases in bone mineral density (BMD) at the lumbar spine and hip [6].

Although elevated body mass index (BMI) is associated with worse breast cancer survival [1], a high BMI correlates strongly with BMD and may be protective for bone health [21, 33]. Further, weight loss results in bone loss in obese older adults and is associated with reductions in BMD at clinically important sites of fracture [30, 31]. In postmenopausal women without cancer, a 1 pound decrease in weight is associated with modest, clinically meaningful decrease in BMD and an increase in circulating osteocalcin concentrations [2]. Nevertheless, the impact of weight loss on bone health in postmenopausal breast cancer survivors is not well known. Because current guidelines recommend weight loss in obese cancer survivors[23], it is essential to establish the impact of weight loss on bone health in overweight/obese postmenopausal breast cancer survivors. This will allow for personalized weight control recommendations in breast cancer survivors. In this study, we investigated the associations of weight loss on BMD and bone turnover markers (BTMs) among overweight/obese postmenopausal breast cancer survivors enrolled in a weight loss trial.

Methods

Study Population

We conducted this study in a subset of women (postmenopausal, N=81) enrolled at the St. Louis site of the Exercise and Nutrition to Enhance Recovery and Good health for You (ENERGY) study. The ENERGY study is a randomized controlled clinical trial designed to achieve a sustained ≥7% loss in body weight at 2 years among 800 overweight or obese

(BMI >27 and <40 kg/m^2) women aged 21 and older diagnosed with stage I (>1 cm), II, or IIIA breast cancer [22]. Detailed description of this study population and the enrolled participants is reported elsewhere [22]. To be eligible, the women must have been diagnosed between 6 months and 5 years prior to enrollment. In addition to St. Louis, the other clinical sites taking part in the ENERGY study are; University of California, San Diego; University of Colorado Denver; University of Alabama at Birmingham.

This report describes a sub-study conducted among postmenopausal women enrolled in the ENERGY study at the St. Louis clinical site. We used a modification of the National Comprehensive Cancer Network (NCCN) postmenopausal definition that doesn't require measurement of serum hormone levels. A woman was considered postmenopausal if she had either a prior bilateral oophorectomy, is age 60 or older, or if under age 60, has been amenorrheic at least 12 months [18]. We approached all postmenopausal women scheduled for a baseline ENERGY study visit and invited them to participate in this study after consenting to the parent ENERGY trial. No additional eligibility or exclusion criteria were applied beyond willingness to participate in the supplemental data collection and participants completed a second consent to participate in this ancillary study. This study was approved by the Washington University in St. Louis IRB.

Interventions and outcomes

The primary outcome of the ENERGY trial is weight loss with a secondary aim of improved quality of life. The intervention consisted of cognitive-behavioral therapy for obesity, increased physical activity, and individualized diet modification that promotes an energy deficit [22]. Participants were assigned to an evidence-based intensive weight loss intervention or a minimal contact health promotion intervention that addresses weight, diet and exercise among other components of healthy survivorship through standard materials. Weight loss was achieved largely through dietary modification designed to promote a reduction in energy intake relative to expenditure aiming for a 500–1000 kcal/day deficit relative to expenditure to attain a weight loss of 1–2 pounds/week, with the addition of physical activity. Lower energy density of the diet was accomplished by advocating high-fiber vegetables, whole grains, and fruit to add bulk and weight to the diet, as these changes promote maximal satiety while reducing energy intake [22].

Other measurements

Body mass index—Height was measured at baseline, and weight was measured at baseline, 6 months and 12 months using a calibrated scale. Height and weight were used to calculate BMI (kg/m^2).

Bone mineral density (BMD)—Dual energy X-ray absorptiometry (DXA) scan was used to assess T-score, lumbar and pelvis BMD at the time of baseline examination and at 12 months follow-up. DXA scan was performed at the Clinical Research Unit (CRU), a component of the Center for Applied Research Sciences (CARS) within the Institute of Clinical and Translational Sciences (ICTS), Washington University School of Medicine, St. Louis, MO.

Bone turn over markers (BTMs)—Markers of bone formation: osteocalcin (ng/mL), bone-specific alkaline phosphatase (BALP, ug/L), procollagen type I N-terminal propeptide (PINP, ng/mL) and bone resorption: N-telopeptides of type-I collagen (NTx, nM BCE/L), C-terminal telopeptide (CTX, ng/mL) were quantified in fasting blood samples collected at baseline, 6 month and 12-month follow-up. In addition, we quantified regulators of bone remodeling; receptor activator factor–kappa B (RANK, pg/mL), and its ligand (RANKL, pmol/L). Serum samples were stored at −80°C within 1 hour of collection at the Tissue Procurement Core, Washington University School of Medicine, St. Louis, MO.

Laboratory analyses

Bone turn-over markers were assayed at the Center for Clinical and Translational Research at the Maine Medical Center Research Institute, Maine. PINP, CTX, BALP, osteocalcin were assayed using iSYS Analyzer (Luminescence) while NTx, RANK, and RANKL, were assayed using enzyme linked immunosorbent assays (ELISA). Baseline, 6-month, and 12-month follow-up serum samples for each participant were analyzed at the same time, in the same analytic batch to eliminate interbatch variation in analyte concentrations and assay drift bias. The interassay and intra-assay variabilities were; PINP (4.6%, 2.6%), CTX (6.2%, 3.2%), BALP (7.3%, 1.6%), osteocalcin (6.1%, 2.5%), NTx (6.9%, 4.6%), RANK (4.2%, 3.7%), and RANKL (4.8%, 3.6%).

Statistical Analysis

Descriptive statistics were generated for participants' demographics and baseline calculated values including percentages for categorical variables (age group, race, marital status, education level, baseline BMI group, cancer stage, tumor grade, tumor type, clinical treatment, ER, PR, and Her2 status) and means for continuous variables (age).

Data from intervention and control arm women were used and treated as a cohort. The outcomes include weight loss, change in BMD, and change in BTMs (osteocalcin, CTX-I, PINP, BALP, NTx) as well as RANK and RANKL. Potential outliers were identified for the change of each outcome at each post-baseline visit using the Rosner outlier algorithm [24]. The following analyses were performed on the observations after the outliers were removed.

Pearson correlations were calculated to measure the relation between changes from baseline in weight with BTM changes at 6 and 12months and BMD changes at 12 months. The generalized estimating equation (GEE) model was used to analyze the longitudinal data, in which the correlation among the repeated measures from the same patient are considered. The outcomes (weight loss, BTM changes) were evaluated through the GEE model to assess whether the average scores were the same over time and whether the average score at post-baseline (month 6 and 12) differed from that at baseline. Standard errors were calculated within the use of a GEE sandwich method when accounting for within-patient correlation. All analyses were conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

Results

The mean age at enrollment among women in our sub-study was 56 years (Table 1). The mean BMI was 31.6kg/m^2. Thirty nine percent (N=32) were overweight (BMI 25–29.9kg/m^2), 36% (N=29) had a BMI between 30–35kg/m^2 and 24.7% (N=20) had a BMI >35kg/m^2 respectively. The majority (54%) had stage II disease. Twenty-six percent (26%) were treated with tamoxifen and 54% were treated with an aromatase inhibitor.

There were no correlations between weight change from baseline to 6 months and changes in BTMs over the same period (Table 2). Change in PINP was strongly correlated with changes in other markers of bone formation; osteocalcin (r=0.69, p-value<0.01) and BALP (r=0.53, p-value<0.01). Weight change at 12 months was weakly inversely correlated with change in T-score (r=−0.25, p-value=0.04) but positively correlated with change in RANK concentrations (r=0.26, p-value=0.04). Further, changes in T-score and lumbar spine BMD were weakly inversely correlated with changes in BALP (r=0.29, p-value=0.02) and RANK (r=−0.27, p-value=0.04), concentrations.

We evaluated whether the mean scores post-baseline (months 6 and 12) differed from those at baseline (Table 3). Mean weight in pounds decreased by 3% and 2.3% pounds between baseline and 6-month, and 12-month follow-up, respectively (p-values<0.01). There was a 6.3% increase (p-value=0.03) in BALP concentrations between baseline and 6 months, which became attenuated at 12 months (3.5%, p-value=0.21). RANK concentrations decreased by 43% and 48.5% (p-values<0.01) at 6 months and 12 months, respectively. On the other hand, significant changes in some BTMs were only observed at 12 months. Osteocalcin, PINP, and NTx levels decreased by 10.6%, 14.5% and 19.2% (p-values<0.01) respectively, between baseline and 12 months compared with 2.7%, 0.6%, and 3.4%, respectively, between baseline and 6 months. There were no changes in T-scores, BMD pelvis and lumbar spine over the 12-month study period. Nevertheless, there was a reduction in T-score (from 0.93 to 0.78, p-value 0.20) among overweight women but an increase among obese women (from 0.88 to 1.00, p-value=0.27) (**Data not shown**). Twenty-eight women (35% of study population) lost >5% of their body weight over the 12-month study period.

Discussion

Weight loss over 12-months, but not over 6-months was associated with a decrease in BTMs in overweight/obese postmenopausal women with stage I, II or IIIA breast cancer, but no associated changes in BMD were observed.

To the best of our knowledge, this is the first study to prospectively evaluate the effect of intentional weight loss on BTMs in overweight/obese postmenopausal breast cancer survivors. Increase in BTMs is associated with bone loss, with a 2-fold increased rate of loss associated with 1 standard deviation increase in some BTMs [25]. In our study, weight loss was not associated with an increase, but rather a decrease in some BTMs, contrary to what has been described in overweight/obese non-cancer populations[12, 13, 30, 31]. In a small study of 48 adults (18 men and 30 women) with a mean BMI of 27 kg/m^2 at enrollment;

those assigned to caloric-restriction experienced a >8% weight loss over the 1-year intervention period [30]. Caloric restriction-induced weight loss was associated with statistically significant reductions in BMD at the lumbar spine (−2.2%) and total hip (−2.1%), but not with total body BMD. There was an increase in circulating CTX levels at 6 months, but not at 1 year and no changes in BALP and osteocalcin levels were observed [30]. In another study (N=37), which involved very low-energy diet induced weight loss over 3 months followed by weight maintenance over 9 months, weight loss (−16%) over 1 year was associated with an increase in CTX (18%) and osteocalcin (26%) levels [12]. These studies, however, differ from ours since they were conducted among people without cancer and they were comparatively smaller-sized. In addition, the magnitude of weight loss in our study population was smaller (a 2.3% decrease from baseline to 12 months) compared with what was reported in these studies. It is possible that the magnitude of weight loss observed in our study might have beneficial, rather than deleterious effect on bone health but this will need to be confirmed in studies where participants experience a similar magnitude of weight loss as in our study.

A few studies have evaluated the effect of exercise on bone health in breast cancer survivors but the impact on weight was not reported. Women assigned to strength/weight training exercise plus medication (calcium, vitamin D and risedronate) demonstrated an increase in BMD total hip and spine, as well as a decrease in BALP (20.6%) and NTx (18.3%) concentrations between baseline and 12 months [32]. The magnitude of decrease in NTX is similar to what we observed in our study population over the same 12-month period (19%). Likewise, in a very small study, women (N=7) assigned to Tai Chi Chuan, a moderate form of weight-bearing exercise for 12 months achieved a 37% decrease in NTx and a 22% increase in BALP concentrations [20]. The very small size of this study, however, limits interpretation of study findings. Although, we observed a 6% increase in BALP concentrations at 6 months, this was attenuated to 3.5% at 12 months.

Bone is a metabolically active tissue undergoing continuous remodeling characterized by bone formation and bone resorption [28]. Bone mass depends on the balance between resorption and formation [28]. This is reflected in BMD and within the circulation in BTMs. DXA is the best densitometric technique for assessing BMD [15]. One standard deviation decrease in BMD measured by DXA is associated with a 2-fold increased risk of hip and spine fracture [4]. DXA, however, is a relatively static measure that doesn't capture ongoing bone loss or remodeling as detectable changes in BMD using DXA scan can take up to 2 years to become apparent [16]. Further, the average individual annual change in DXA score (≈1%) is often very small and could be of the same magnitude as that arising from random measurement variation [7].

Conversely, BTMs reveal acute changes in bone metabolism compared with DXA. The most sensitive markers of bone formation are osteocalcin, BALP and PINP while breakdown products of type I collagen fragments; CTX and NTx are established markers of bone resorption [8]. Circulating osteocalcin and BALP levels reflect the cellular activity of osteoblasts while PINP levels reflect changes in synthesis of new collagen [19]. Further, normal bone remodeling is regulated by the receptor activator factor–kappa B ligand (RANKL) pathway [14, 17]. Increase in BTMs can identify women at a high risk of bone

loss and subsequent fracture, particularly hip and vertebra fractures [9, 10, 26, 29]. Because BTMs provide independent prediction of fracture risk, and changes in BTMs become apparent before changes in BMD appear [11], it has been suggested that bone health might be evaluated using BTMs, independent of BMD [16], but debate on this is still ongoing.

In conclusion, our study suggests that a 2.3% weight loss over 12 months does not appear to have deleterious effect on bone health, and might even be beneficial, among overweight/obese women with early stage breast cancer. However, because changes in BTM appear before changes in BMD, studies with longer follow-up are needed to characterize the effect of weight loss on BMD among breast cancer survivors. Further, studies that evaluate the possible modifying effect of physical activity on weight loss and bone health are needed in order to personalize weight control strategies in overweight/obese breast cancer survivors.

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Table 1

Baseline characteristics of postmenopausal women with breast cancer (N=81) enrolled in the Bone Health Study, Washington University School of Medicine, St. Louis

Characteristic	
Age, years	56.1 (9.3)
Body mass index (BMI), kg/m2	31.6 (5.0)
25–29.9	32 (39.5)
30–35	29 (35.8)
>35	20 (24.7)
T-score	0.90 (1.7)
Lumbar spine bone mineral density	1.08 (0.2)
Pelvis bone mineral density	1.21 (0.2)
Race	
White	71 (87.7)
Black	10 (12.3)
Education	
High school Graduate	12 (14.8)
Some College	23 (28.4)
College	22 (27.2)
Post-Graduate	24 (29.6)
Tumor Stage	
Stage 1	24 (29.6)
Stage 2	44 (54.3)
Stage 3	13 (16.1)
Tumor grade	
Well differentiated	18 (22.2)
Moderately differentiated	31 (38.3)
Poorly differentiated	27 (33.3)
Unspecified	5 (6.2)
Treatment with Tamoxifen	
Yes	21 (25.9)
No	60 (74.1)
Treatment with an Aromatase Inhibitor	
Yes	44 (54.3)
No	37 (45.7)

Continuous variables are presented as mean (standard deviation) and categorical variables are presented as frequency (percentages).

Table 2

Correlations of weight change from baseline to 6 and 12 months with changes in bone turn over markers and bone mineral density over the same period

	Weight change	BALP	Osteocalcin	PINP	CTX	NTX	RANK	RANKL	T-score	BMD Lumbar	BMD Pelvis
At 6 months											
Weight change	1.00	0.09 0.48	−0.06 0.64	−0.17 0.15	−0.10 0.43	−0.18 0.14	0.13 0.35	−0.11 0.38	N/A	N/A	N/A
BALP		1.00	**0.44** **<0.01**	**0.53** **<0.01**	**0.26** **0.03**	0.03 0.78	0.12 0.37	−0.02 0.87	N/A	N/A	N/A
Osteocalcin			1.00	**0.69** **<0.01**	**0.37** **<0.01**	0.00 0.97	0.11 0.40	−0.06 0.66	N/A	N/A	N/A
PINP				1.00	**0.35** **<0.01**	0.01 0.94	0.05 0.73	0.04 0.74	N/A	N/A	N/A
CTX					1.00	0.08 0.53	−0.05 0.72	−0.20 0.13	N/A	N/A	N/A
NTX						1.00	0.02 0.90	0.01 0.96	N/A	N/A	N/A
RANK							1.00	−0.13 0.35	N/A	N/A	N/A
RANKL								1.00	N/A	N/A	N/A
At 12 months											
Weight change	1.00	0.18 0.15	−0.04 0.74	−0.17 0.15	−0.22 0.07	0.02 0.90	**0.26** **0.04**	−0.15 0.23	**−0.25** **0.04**	−0.21 0.08	0.14 0.25
BALP		1.00	**0.31** **0.01**	**0.37** **<0.01**	**0.27** **0.02**	−0.08 0.49	−0.06 0.67	−0.08 0.51	**−0.29** **0.02**	0.03 0.81	−0.21 0.09
Osteocalcin			1.00	**0.64** **<0.01**	**0.37** **<0.01**	−0.01 0.90	0.05 0.73	0.18 0.17	0.07 0.56	0.04 0.74	−0.02 0.87
PINP				1.00	**0.51** **<0.01**	−0.02 0.87	−0.08 0.53	0.03 0.83	−0.12 0.32	−0.14 0.24	−0.01 0.93
CTX					1.00	0.02 0.89	−0.03 0.80	−0.11 0.38	0.07 0.55	0.05 0.65	0.04 0.76
NTX						1.00	0.09 0.48	−0.04 0.76	−0.03 0.81	0.04 0.76	0.05 0.68
RANK							1.00	−0.01 0.93	−0.03 0.81	**−0.27** **0.04**	0.12 0.37
RANKL								1.00	0.06 0.64	0.01 0.94	−0.18 0.16

T-score									1.00	0.05 0.65	0.15 0.22
BMD Lumbar										1.00	0.08 0.51
BMD Pelvis											1.00

P-values are presented below the Pearson correlation coefficients

BALP - bone-specific alkaline phosphatase
PINP - procollagen type I N-terminal propeptide
NTX - N-telopeptides of type-I collagen
RANK - receptor activator factor–kappa B
RANKL - receptor activator factor–kappa B ligand
BMD – Bone mineral density
N/A Not Available

Table 3

Changes in weight, bone turn over markers and bone mineral density from baseline*

	Baseline	6 months	Change	% Change	P-value	12 months	Change	% Change	P-value
Weight, lbs.	189.15	183.58	−5.57	−2.95 %	<0.01	184.90	−4.25	−2.25 %	<0.01
BALP, ug/L	16.87	17.94	1.07	6.34%	0.03	17.46	0.59	3.50%	0.21
Osteocalcin, ng/mL	19.10	18.58	−0.52	−2.72%	0.29	17.08	−2.02	−10.58%	<0.01
PINP, ng/mL	54.67	54.37	−0.30	−0.55%	0.89	46.73	−7.94	−14.52%	<0.01
CTX, ng/mL	0.58	0.59	0.01	1.72%	0.65	0.55	−0.03	−5.17%	0.26
NTX, nM BCE/L	19.05	18.40	−0.64	−3.36%	0.54	15.39	−3.65	−19.16%	<0.01
RANK, pg/mL	28.00	15.95	−12.05	−43.04%	<0.01	14.42	−13.58	−48.50%	<0.01
RANKL, pmol/L	146.40	150.77	4.37	2.98%	0.65	125.66	−20.74	−14.17%	<0.01
T-score	0.90					0.89	0.01	1.11%	0.88
BMD Lumbar	1.08					1.09	−0.01	−0.93%	0.58
BMD Pelvis	1.18					1.17	0.01	0.85%	0.46

* Mean estimates and p-values based on Generalized Estimating Equation models

BALP - bone-specific alkaline phosphatase
PINP - procollagen type I N-terminal propeptide
NTX - N-telopeptides of type-I collagen
RANK - receptor activator factor–kappa B
RANKL - receptor activator factor–kappa B ligand
BMD – Bone mineral density