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Effects of Weight Loss and Weight Regain on Circulating Biomarkers in Overweight/Obese Breast Cancer Survivors Enrolled in a Weight Loss Trial in the Rural Midwest

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ABSTRACT

Background: Obesity is associated with worse breast cancer prognosis, however little is known about the level of weight loss required to improve pathway biomarkers. The effects of weight regain on biomarkers are also largely unknown.

Methods: Overweight/obese breast cancer survivors enrolled in an 18-month behavioral weight loss trial provided weight and serum biomarkers [leptin, adiponectin, insulin, plasminogen activator inhibitor-1 (PAI-1), IL-6, TNFα, and hepatocyte growth factor HGF] at baseline, 6, and 18 months ($n = 138$). Change in biomarkers over time and by weight loss thresholds were examined.

Results: Mean weight loss at 6 months was 13.3 ± 5.0 kg; from 6 to 18 months, mean regain was 4.0 ± 5.2 kg. Favorable biomarker modulations were observed at 6 months for leptin, adiponectin, insulin, PAI-1, IL-6, and HGF ($P < 0.006$ to $P < 0.0001$). These changes remained significant overall at 18 months despite attenuation in some. Women who lost <10% of baseline weight showed significantly smaller modulation effects for leptin ($P < 0.0001$), adiponectin:leptin (A/L) ratio ($P < 0.0001$), PAI-1 ($P < 0.001$), and insulin ($P = 0.003$) compared with women who lost >10%. Women who lost >10% observed a significant increase in adiponectin ($P < 0.0001$), and these women continued to show improved adiponectin from 6 to 18 months despite weight regain. Physical activity contributed additional effects on biomarker change for leptin, A/L ratio, and PAI-1.

Conclusions: These findings are consistent with a clinical target of 10% weight.

Impact: Sustained increases in adiponectin likely confer benefits for breast cancer prognosis even with weight regain.

Introduction

Obesity and physical inactivity are associated with increased mortality from breast cancer and cardiovascular disease (1, 2), the two most common causes of death in postmenopausal women with a breast cancer diagnosis (3, 4). Over two-thirds of breast cancer survivors are overweight or obese (5) and do not meet physical activity guidelines (6, 7). At present, it is not clear whether weight loss improves breast cancer survival in overweight and obese women although this is the outcome of an ongoing randomized trial (8). Changes in systemic hormonal, cytokine, adipokine, and insulin pathway biomarkers influenced by weight loss and physical activity may help define both the necessary weight loss and the influence of regain on likelihood of cancer recurrence.

Studies in obese women without cancer suggest a 10% loss from baseline reliably modulates most of these biomarkers (9) and is in line with general weight loss guidelines that recommend 5% to 10% loss (10). However, there is almost no information about the effect of weight regain on biomarkers. Without extended intervention, 30%–50% of weight loss is typically regained within one year (11), and most individuals will regress to their baseline weight within 5 years (12, 13).

The purpose of this secondary analysis is to examine the impact of weight loss and weight regain on change in insulin, leptin, adiponectin, adiponectin-leptin ratio (A/L ratio), IL-6, TNFα, plasminogen activator inhibitor-1 (PAI-1), and hepatocyte growth factor (HGF) among postmenopausal women with a history of breast cancer who participated in a behavioral randomized controlled trial targeting weight loss at 6 months followed by 12 months of weight loss maintenance (14). These biomarkers are implicated in breast cancer recurrence, cardiovascular disease, or both. We also explored the additive effect of moderate-to-vigorous physical activity (MVPA) on biomarker change.

Methods

The trial enrolled rural postmenopausal breast cancer survivors into an 18-month intervention. A detailed description of the study protocol, intervention, and weight loss outcomes have been published previously (14, 15). In brief, the trial included a two-phase intervention, including a nonrandomized weight loss phase where all participants received a 6-month behavioral weight loss intervention delivered via weekly group conference calls, and a 12-month weight loss maintenance phase (from 6 to 18 months) where women were randomized 1:1 to extended care either through continued biweekly group conference calls or biweekly mailed newsletters. The main findings of the trial showed a mean 14% weight loss at 6 months, and that participants randomized to continued biweekly conference calls for extended care had a significant reduction in weight regain from 6 to 18 months compared with women randomized to biweekly newsletters (net reduction of 1.6 kg; ref. 15). Participants from both extended care

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conditions are included in these secondary analyses. The University of Kansas Medical Center Human Subjects Committee approved all study procedures. Written informed consent was obtained from each participant, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

Participants were postmenopausal female breast cancer survivors who were ≤75 years old, had a body mass index (BMI) of 27–45 kg/m^2, lived in a rural area (16, 17), had been diagnosed with Stage 0–IIIc breast cancer within the past 10 years (except stage 0 with mastectomy only), had completed surgery, radiation, and chemotherapy at least 3 months prior to entry, and obtained clearance from their oncologist or primary medical provider to participate. Women with pending joint replacements, serious cardiac or pulmonary conditions, insulin-dependent diabetes, history of bariatric surgery, current substance abuse (18), major depression (19), or binge eating disorder (20) were excluded. Participants had to be able to walk unassisted, be weight stable within ten pounds over past 3 months, and not be participating in another weight loss program or using pharmacotherapy for weight loss.

Among 210 women who were enrolled in the trial, 205 had biomarker assay measures at baseline. During the 6-month weight loss phase, 6 participants were removed for recurrence or medical reasons, and 13 were lost to follow-up. Of the remaining 191 participants, 179 had blood for biomarker assays at baseline and 6 months. From 6 to 18 months, 4 participants were removed for recurrence or medical reasons, and 14 were lost to follow-up. Of the remaining 169 participants who attended the 18-month visit, 138 had biomarker measures at all three timepoints (see Supplementary Fig. S1 showing participant flow).

Intervention

The initial 6-month weight loss intervention was delivered by a trained group leader (registered dietitian or psychologist) via weekly 60-minute conference calls in groups of 12 to 15 women. Participants were instructed to consume a 1,200–1,500 kcal/day diet and to gradually increase moderate intensity physical activity up to 225 minutes per week (21). To facilitate adherence to calorie goals, participants were instructed to purchase and consume approved prepackaged frozen entrees available in their local grocery stores (<350 kcal each) or their equivalent, and to add at least 5 one-cup fresh or frozen fruit and vegetable servings and calorie-free beverages. In addition, participants were provided with two meal replacement shakes per day to aid weight loss for the first 6 months (22). Group leaders helped to tailor these dietary recommendations to fit individual participant's preferences. To facilitate adherence to physical activity, participants were given a toolkit including a pedometer, home-based physical activity DVDs, and an opportunity to earn additional physical activity incentives (e.g., walking shoes, water bottles) by meeting physical activity goals. Participants kept daily self-monitoring records and set weekly diet and physical activity goals. Intervention sessions included special topics related to breast cancer risk, managing late side effects, and body image, as well as topics that addressed rural access barriers and cultural food preferences.

During the weight loss maintenance phase, all participants were given a new calorie goal calculated from Harris–Benedict formula to sustain their reduced body weight (23), and were encouraged to continue to purchase and consume up to 2 shakes or prepackaged entrees per day, to maintain their physical activity goal, and to continue to self-monitor diet and physical activity. Participants randomized to continued group phone counseling received biweekly conference call sessions that incorporated a social cognitive approach to relapse prevention using problem-solving (24) as well as review of nutrition, exercise, and behavioral topics. Participants in the mail condition received newsletters at the same frequency as the phone sessions. The newsletters covered the same educational content as the phone arm.

Measures

Weight was measured and blood samples collected at baseline, 6, and 18 months. Participants were weighed in light clothing using a calibrated scale accurate to 0.1 kg (Befour PS5700). Assays were conducted for biomarkers that are linked to pathways of insulin resistance (insulin) and adipose tissue inflammation (leptin, adiponectin, A/L ratio, IL-6, TNFα, HGF, and PAI-1). A ≥12-hour fasting blood draw was performed by a licensed phlebotomist, processed into serum aliquots, and stored at −80°C until assays were run. Serum levels of cytokines/adipokines were determined using Milliplex MAP kits obtained from EMD Millipore Sigma Corporation. Adiponectin and PAI-1 were assayed using Human Adipokine Magnetic Bead Panel 1 (HADK1MAG-61K); leptin, insulin, IL-6, TNFα, and HGF were assayed using Human Adipokine Magnetic Bead Panel 2 (HADK2-MAG-61K). All assays were performed according to the kit protocols. Samples for all timepoints were run together to avoid batch variation and all assays were performed in duplicate, with mean coefficients of variation as follows: adiponectin (2.7%), leptin (3.4%), PAI-1 (7.3%), IL-6 (4.3%), insulin (4.5%), HGF (4.5%), and TNFα (3.9%)

Physical activity was measured with a GT3X+ Actigraph Accelerometer (Fort Walton Beach, FL) worn for seven consecutive days at each assessment point. Accelerometry data were included if data was available for ≥10 hours/day for ≥4 days (25). MVPA minutes (counts ≥1952 per min for at least 8 consecutive minutes) per valid day were calculated and multiplied by 7 to obtain weekly estimates (26, 27).

Statistical analyses

Analyses are based on relative changes to minimize the effect of baseline levels. To visualize the marginal relative change of each biomarker across the full spectrum of weight loss, we used a restricted natural cubic spline with 4 equally spaced knots (28). To estimate the 95% pointwise confidence interval of each curve/spline, we used the percentile bootstrap with 1,000 bootstrap samples. To derive a plausible cutoff point, we used an algorithm to scan with a fine grid with (0.001 step) in the region of 5%–15% weight loss from 0 to 6 months, and 2%–8% regain from 6 to 18 months. We selected the cutoff point that corresponded to the highest difference in the median relative biomarker change.

The impact of a priori potentially relevant covariates (age, cancer stage, current antihormone therapy, history of chemotherapy, time since cancer treatment, and randomized intervention arm from 6 to 18 months) was modeled using generalized estimating equation (GEE) regression analyses under the Markov correlation structure using the log transformation for each biomarker as the dependent variable and weight as the independent variable. Results remained similar between adjusted and unadjusted models (see Supplementary Tables S1 and S2). Therefore, results are shown without adjustment for covariates.

Nonparametric Wilcoxon signed rank test was used for assessment of change in biomarkers over the course of the intervention. Nonparametric Mann–Whitney test was used for comparison between groups dichotomized by weight loss/regain thresholds. GEE regression models were used to explore the potential additive effect of MVPA on biomarkers while accounting for weight change. Results for 0 to 6 months and from 6 to 18 months are presented. Analyses were

conducted using SPSS, version 24 and MATLAB 2019a. For evaluation of the seven serum biomarkers (plus A/L ratio) conducted in parallel, a modified Bonferroni correction was used, with a criterion for significance of <0.006 (i.e., 0.05/8).

Results

Participant characteristics

Baseline characteristics for the 138 participants who had weight and serum specimen available at all three timepoints are summarized in **Table 1**. At baseline, participants were on average 58.8 ± 7.9 years old, 3.5 ± 2.4 years since breast cancer treatment, and had a BMI of 34.1 ± 4.2 kg/m^2. Women were primarily diagnosed with stage 1 (46%) or stage 2 (33%) breast cancer. The average loss at 6 months was 13.3 ± 5.0 kg with 109 (79%) losing >10% and all losing >5% of baseline weight. At 18 months, the average weight loss was 9.3 ± 7.3 kg from baseline; 72 (52%) maintained at least a 10% loss below baseline and 93 (67%) maintained at least 5% below baseline. Baseline characteristics were similar between the cohort of 138 with biomarkers at all three time points versus the 179 with biomarkers at baseline and 6 months only (See Supplementary Table S3).

Change in serum biomarkers

As shown in **Table 2**, there were statistically significant favorable modulations over the first 6 months for adiponectin, leptin, A/L ratio, insulin, PAI-1, HGF, and IL-6 but not TNFα. Adiponectin and A/L ratio exhibited significant median increases of 15% and 224%, respectively ($P < 0.0001$). Leptin, PAI-1, and insulin demonstrated significant median decreases of −65%, −19%, and −37%, respectively ($P < 0.0001$). Relative decreases in IL-6 and HGF were more modest but still statistically significant ($P < 0.006$). At 18 months there continued to be favorable modulation of biomarkers. Adiponectin and IL-6 showed continued improvement from 0 to 18 months compared with that from 0 to 6 months. There was little difference in PAI-1 and HGF for change from 0 to 18 months compared with 0 to 6 months. Leptin and insulin worsened between 6 and 18 months resulting in an attenuation of the 0- to 18-month change compared with that between 0 and 6 months.

There was little difference in biomarker change during the first 6 months between the cohort of 138 with biomarkers at all three time points versus the 179 with biomarkers at baseline and 6 months only (See Supplementary Table S4).

Relative biomarker change by percent weight loss

Visualization of relative biomarker change by relative weight change revealed justification for deriving weight loss cutoff points for adiponectin, leptin, and A/L ratio (see Supplementary Fig. S2 for cubic spine plots). For PAI-1, insulin, and IL-6 the trend was linear, thus no cutoff point selection was appropriate. For HGF and TNFα, no association was observed. Derived cutoff points for weight loss from 0–6 months were 9.0% for adiponectin, 8.0% for leptin, and 15.0% for A/L ratio. Derived cutoff points for weight regain from 6 and 18 months were 2.1% for adiponectin, 2.2% for leptin, and 2.0% for A/L ratio.

Change in serum biomarkers by 6-month weight loss category

We compared relative biomarker change for women who lost >10% versus <10% during the 6-month weight loss phase based on clinical guidelines (10) and consistent with the sample derived cutoff points for adiponectin and leptin. As shown in **Table 3** and **Fig. 1** (and Supplementary Table S5), women who lost >10% but not those who lost <10% observed a significant increase in adiponectin ($P < 0.0001$).

Table 1. Participant characteristics ($n = 138$).

	Mean (SD) or *n* (%)
Age, years	58.8 (7.9)
Baseline weight, kg	91.0 (13.2)
Baseline BMI, kg/m^2	34.1 (4.2)
Waist circumference, cm	99.3 (9.9)
Waist–height ratio	0.61 (0.06)
Rurality[a]	
Large rural	82 (45%)
Small/isolated rural	76 (55%)
Time since treatment, y	3.5 (2.5)
Cancer stage	
0	11 (8%)
I	64 (46%)
II	46 (33%)
III	17 (12%)
Education	
High school/GED	30 (22%)
Some college	55 (40%)
Bachelor's degree	31 (23%)
Master's degree/doctorate	22 (16%)
Race/ethnicity, Caucasian	137 (99%)
Marital status	
Married/cohabitating	118 (86%)
Single/divorced	11 (8%)
Widowed	9 (7%)
Employment	66 (48%)
Full-time	
Part-time	33 (24%)
Retired/not employed	39 (28%)
Breast cancer treatment history	
Mastectomy	63 (46%)
Lumpectomy	75 (54%)
Chemotherapy	89 (64%)
Radiation	98 (71%)
Current antihormone therapy	80 (58%)
Weight change 0 to 6 months, kg	−13.3 (5.0)
Relative to baseline, %	−14.6 (5.2)
Weight change 6 to 18 months, kg	4.0 (5.2)
Relative to 6 months, %	4.0 (6.4)
Weight change 0 to 18 months, kg	−9.3 (7.3)
Relative to baseline, %	−10.3 (7.9)

Abbreviations: BMI, body mass index; GED, general equivalency diploma.
[a]On the basis of rural–urban commuting area codes.

In addition, women who lost <10% (5%–10%) of baseline weight at 6 months saw significantly smaller biomarker modulation effects for leptin ($P < 0.0001$), A/L ratio ($P < 0.0001$), PAI-1 ($P < 0.001$), and insulin ($P = 0.003$) compared with women who lost >10% of baseline weight.

Change in serum biomarkers by 6- to 18-month weight regain category

We examined change in biomarkers from 6 to 18 months by the median weight regain cutoff point of 5% of 6-month weight. To avoid confounding with the amount of initial weight loss, analysis from 6 to 18 months was restricted to the 109 participants who had lost at least 10% of baseline weight at 6 months (**Table 3**). Mean weight change from 6 to 18 months for those who regained >5% ($n = 54$) was 7.9 ± 3.9 kg, compared with −0.2 ± 3.5 kg in those who regained <5% [$n = 55$; of whom 20 (36%) showed a loss and 35 (64%) showed a gain]. As shown in **Table 4** and **Fig. 2**, the >5% weight regain group exhibited

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Table 2. Values for serum biomarkers at baseline, 6 months, and 18 months and relative difference (percent) over time ($n = 138$).

				Relative difference, %		
	Baseline	6 months	18 months	Baseline to 6 months	6 to 18 months	Baseline to 18 months
Serum biomarker	Median (interquartile range)			Median		
Adiponectin (μg/mL)	27.9 (16.8–45.4)	33.9 (19.7–50.7)	38.2 (22.5–61.8)	15[a]	20[a]	38[a]
Leptin (ng/mL)	44.1 (28.2–62.6)	14.5 (7.8–29.2)	29.9 (11.6–52.7)	−65[a]	68[a]	−35[a]
A/L ratio	666 (330–1321)	1,863 (897–5366)	1,558 (580–4,458)	224[a]	−30[a]	127[a]
PAI-1 (ng/mL)	80.8 (66.8–98.5)	63.5 (51.6–76.7)	67.3 (54.5–82.4)	−19[a]	7[b]	−17[a]
Insulin (pg/mL)	401 (257–608)	234 (150–352)	249 (145–415)	−37[a]	20[c]	−24[a]
IL-6 (pg/mL)	2.29 (1.60–3.91)	2.10 (1.33–3.21)	1.67 (1.10–2.99)	−10[c]	−12[c]	−27[a]
HGF (pg/mL)	510 (364–689)	481 (320–659)	462 (319–588)	−8[c]	−3	−7[c]
TNFα (pg/mL)	4.27 (3.17–5.76)	4.53 (3.21–5.83)	4.58 (3.00–5.68)	0	−2	−4

Note: Significant change by nonparametric Wilcoxon test.
[a]$P < 0.0001$.
[b]$P < 0.001$.
[c]$P < 0.006$.

significant attenuation of initial biomarker changes (worsening scores) for leptin (121% relative increase, $P < 0.0001$), A/L ratio (−46% relative decrease, $P < 0.0001$), PAI-1 (10% relative increase, $P < 0.001$), and insulin (26% relative increase, $P < 0.001$). In contrast, the <5% weight regain group exhibited significant worsening for leptin only (34% relative increase, $P < 0.001$). The 20 women who actually continued to lose weight saw continued favorable modulation of leptin. In both groups, adiponectin continued to show favorable modulation from 6 to 18 months with an 18% relative increase ($P < 0.001$) and 38% relative increase ($P < 0.0001$), in high and low regain groups, respectively. The magnitude of change in adiponectin, leptin, and A/L ratio was significantly different for women who regained less than versus greater than 5% of baseline weight. Changes in PAI-1 and insulin were not statistically significantly different between high and low weight regain groups after adjustment for multiple comparisons.

Effect of moderate-to-vigorous physical activity

GEE models from 0 to 6 months showed significant additive benefit of MVPA, accounting for effects of weight loss, for leptin ($P < 0.0001$), A/L ratio ($P = 0.001$), and PAI-1 ($P = 0.0003$), but not for adiponectin, insulin, IL-6, HGF, or TNFα (see Supplementary Table S6). The effect of weight was significant in the presence of MVPA except for HGF and TNFα. Similarly, from 6 to 18 months, a significant additive benefit of MVPA was observed for leptin, A/L ratio, and PAI-1, but not for the other biomarkers after adjustment for multiple comparisons.

Discussion

Our group phone-based energy balance intervention led to substantial weight loss at 6 months that corresponded to favorable modulation of biomarkers beneficial for breast cancer (29) and cardiovascular risk (30, 31). Significant changes were observed in adiponectin, leptin, A/L ratio, PAI-1, and insulin, as well as significant but less robust changes in IL-6 and HGF. Significant change in adiponectin was observed for women with >10% loss but not <10% loss during the first 6 months. Moreover the magnitude of change in leptin, insulin, and PAI-1 observed for those who lost <10% (5%–10%) was substantially smaller. Lack of robust changes in adiponectin, insulin, PAI-1, and IL-6 with <10% weight loss is similar to that reported in other small trials (9, 32–35). Derived cutoff points were close to 10% for adiponectin (9%), and leptin (8%) and higher for A/L

Table 3. Change (percent relative difference) in serum biomarkers from baseline to 6 months dichotomized by <10% vs. >10% weight loss from baseline to 6 months ($n = 138$).

	<10% weight loss at 6 months ($n = 29$)	>10% weight loss at 6 months ($n = 109$)	
	Median relative difference, %		*P* value between groups[a]
Adiponectin (μg/mL)	3	16[b]	0.060
Leptin (ng/mL)	−38[b]	−68[b]	<0.0001
A/L ratio	62[c]	284[b]	<0.0001
PAI-1 (ng/mL)	−9[d]	−22[b]	0.0007
Insulin (pg/mL)	−30[d]	−42[b]	0.0027
IL-6 (pg/mL)	−5	−11	0.69
HGF (pg/mL)	−11	−7	0.50
TNFα (pg/mL)	1	−1	0.77

Note: Significant change within group by nonparametric Wilcoxon test.
[a]Nonparametric Mann–Whitney test.
[b]$P < 0.0001$.
[c]$P < 0.001$.
[d]$P < 0.006$.

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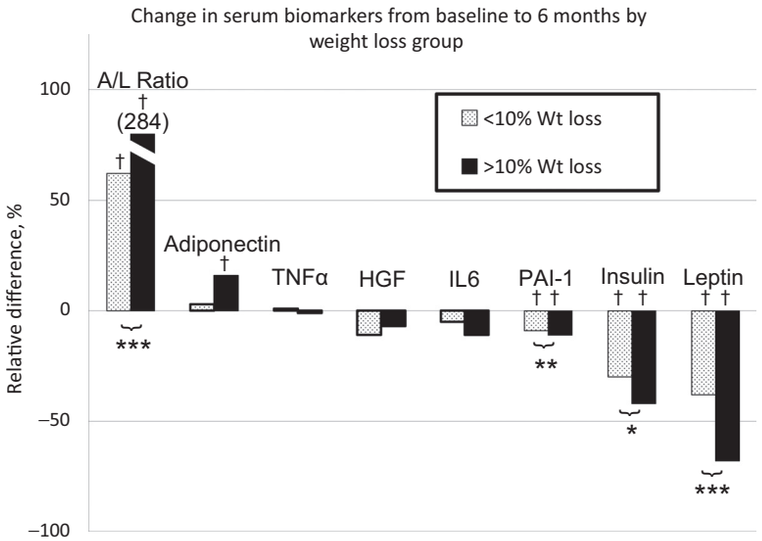

Figure 1.
Changes in biomarkers from baseline to 6 months, dichotomized at the cutpoint of 10% weight loss. † Indicates a statistically significant change within a group (<10% or >10% weight loss, $n = 29$ and 109, respectively). Statistically significant differences between the two groups are indicated by asterisks below bars (*, $P < 0.006$; **, $P < 0.001$; ***, $P < 0.0001$; nonparametric Mann–Whitney test).

ratio (15%), while no clear cutoff point could be discerned for other biomarkers. Overall, our findings are consistent with targeting 10% weight loss. While 5%–10% loss may confer some benefit for certain biomarkers, robust changes are more evident with weight loss that approaches 10% (36).

This is the first study, to our knowledge, to examine change in breast cancer and cardiovascular risk biomarkers during weight regain subsequent to weight loss among breast cancer survivors. The initial favorable biomarker changes remained significant at 18 months, however, there was attenuation with weight regain for leptin and insulin. Interestingly, adiponectin continued to improve during the 12 months after initial weight loss despite weight regain. This has important clinical implications as adiponectin helps protect against insulin resistance and counters the pro-inflammatory effects of leptin (37, 38). There is limited understanding of mechanisms driving these sustained improvements, although continued favorable adipose remodeling/redistribution is likely key.

We found support for an additive benefit of physical activity in the presence of weight change for leptin, A/L ratio, and PAI-1. The lack of an independent effect of physical activity for other biomarkers may be due to inadequate increase in MVPA. In a previous publication, we reported a 6-month increase in MVPA among those who lost >10% but not those who lost <10%, and only the high loss, low regain group (>10% loss, <5% regain) maintained high levels of MVPA through 18 months (109 minutes/week at 18 months compared with 29 minutes/week at baseline and 134 minutes/week at 6 months; ref. 39). The impact of interventions targeting exercise alone on biomarkers in breast cancer survivors has been mixed. A 4-month completely supervised intervention of 150 minutes/week of aerobic activity plus 2–3 days/week of resistance training resulted in significant improvements in leptin as well as insulin, adiponectin, and IL-6 (40). However, this intensive exercise trial also led to 4 kg weight loss, and the relative impact of weight versus physical activity was not reported. In another trial of supervised resistance training 2 days/week, plus 90 minutes of home-based aerobic activity, there was no change in adiponectin or leptin (or weight; ref. 41). Other trials of exercise alone have found a lack of sustained significant changes in insulin (42–44).

Table 4. Change (percent relative difference) in serum biomarkers from 6 to 18 months dichotomized by >5% versus <5% weight regain from 6 to 18 months among subsample with >10% weight loss at 6 months ($n = 109$).

	>5% weight regain ($n = 54$)	<5% weight regain ($n = 55$)	
	Median relative difference, %		*P* value between groups[a]
Adiponectin (μg/mL)	18[b]	38[c]	0.0036
Leptin (ng/mL)	121[c]	34[b]	<0.0001
A/L ratio	−46[c]	11	<0.0001
PAI-1 (ng/mL)	10[b]	1	0.013
Insulin (pg/mL)	26[b]	−4	0.022
IL-6 (pg/mL)	−12[d]	−17[d]	0.48
HGF (pg/mL)	−1	−4	0.11
TNFα (pg/mL)	−2	0	0.50

Note: Significant change within group by nonparametric Wilcoxon test.
[a]Nonparametric Mann–Whitney test.
[b]$P < 0.001$.
[c]$P < 0.0001$.
[d]$P < 0.006$.

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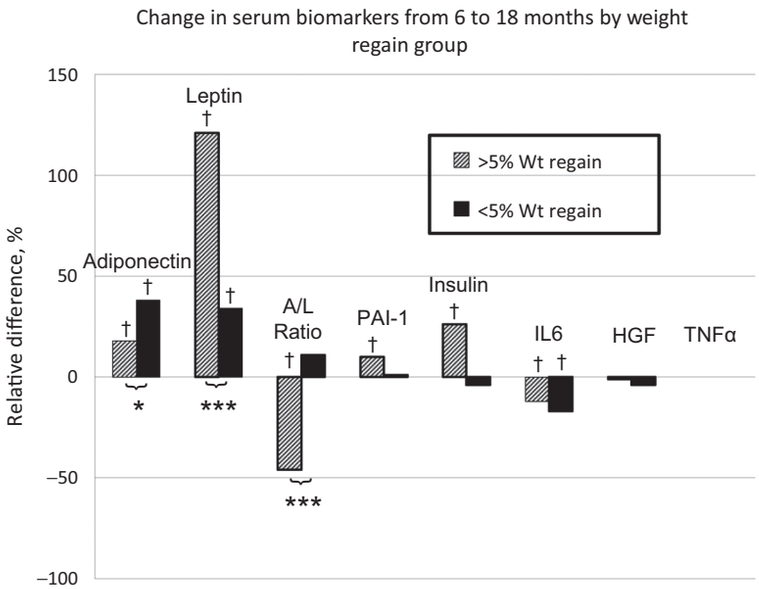

Figure 2.

Changes in biomarkers from 6 months to 18 months, dichotomized at the cutpoint of 5% weight regain at 18 months. † Indicates a statistically significant change within a group (<5% or >5% weight regain, $n = 54$ and 55, respectively). Statistically significant differences between the two groups are indicated by asterisks below the bars (*, $P < 0.006$; **, $P < 0.001$; ***, $P < 0.0001$; nonparametric Mann–Whitney test).

The impact of weight loss followed by weight regain on breast cancer risk biomarkers has received little attention. Bluher and colleagues proposed two distinct patterns of circulating biomarkers in response to weight loss-weight regain trajectories among 322 overweight/obese adults without cancer. The first pattern corresponds tightly to body weight as has been observed with leptin and insulin (45), while the second pattern shows a continued improvement during regain, as has been observed with adiponectin (46). However it is unknown how weight cycling impacts breast cancer prognosis. For cardiovascular risk, some factors such lipids, cholesterol, and blood pressure have been shown to be modified in proportion to final magnitude of weight loss after 2.5 years, regardless of the weight loss–weight regain route taken to achieve the final weight loss (47). However, other factors may influence biomarkers over time and contribute to a drift toward baseline. Beavers and colleagues found that in postmenopausal women who maintained a weight loss within 2 kg over 20 months, initial improvements in insulin and lipids were sustained, whereas blood pressure and glucose tended to return to baseline despite maintenance of weight loss (45).

We observed the greatest relative change for A/L ratio with a 224% increase at 6 months, or a 284% increase among those who lost >10% of baseline weight, which was maintained at 18 months. A/L ratio is a determinant of breast cancer tumorigenesis through multiple mechanisms including cell proliferation, alterations in oxidative stress, and inflammation (48). It has been proposed as a marker of dysfunctional adipose tissue and metabolic syndrome with stronger correlations with insulin resistance and serum amyloid A than adiponectin or leptin alone (49).

We did not find significant reductions in TNFα, and the modest but significant reductions in IL-6 observed in the total sample were not observed in the ±10% weight loss subgroups. This could be due to the smaller sample size in subgroups, ongoing inflammatory processes unrelated to fat mass in some individuals, and unknown timing of last exercise bouts. Changes in inflammatory cytokines are not consistently observed in weight loss trials or related to change in adiposity (46, 50, 51) and may not be robust markers for weight loss clinical trials in older populations taking multiple medications.

Strengths of this study include the relatively large weight losses observed from a remote phone-based lifestyle intervention, high retention for primary data collection (95% at 6 months and 84% retention at 18 months), and sufficient sample size and variability to examine subgroups of meaningful weight loss and weight regain. Limitations of the study include 18% missing serum among those who had weights at all three timepoints, lack of follow-up data beyond 18 months, insufficient numbers of women with lower weight loss/regain to examine biomarker changes across lower cutoff points, and the reliance on statistical significance for detecting meaningful change in biomarkers in the absence of clinically meaningful cutoff points. In addition, the sample represented rural geographic diversity but lacked racial/ethnic diversity, and 54% had very early stage disease (stage 0 to I). The level of weight loss observed, and the corresponding biomarker changes, may not generalize to racial/ethnic minorities and survivors of later stage disease.

In conclusion, findings support the clinical target of 10% weight loss for modulating risk biomarkers. Approaching this level of weight loss appears necessary to modulate adiponectin and has important implications for the overall adipokine milieu including A/L ratio, insulin, and PAI-1. Sustained increases in adiponectin likely confer benefits for breast cancer prognosis even with weight regain.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' Contributions

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