Addition of Exercise Increases Plasma Adiponectin and Release from Adipose Tissue

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ABSTRACT

WANG, X., T. YOU, K. MURPHY, M. F. LYLES, and B. J. NICKLAS. Addition of Exercise Increases Plasma Adiponectin and Release from Adipose Tissue. *Med. Sci. Sports Exerc.*, Vol. 47, No. 11, pp. 2450–2455, 2015. **Introduction**: Adiponectin is an adipose tissue–derived anti-inflammatory protein that is down-regulated in obesity. The effects of caloric restriction and exercise-induced weight loss on adiponectin are not clear. **Purpose**: To determine whether addition of aerobic exercise training to caloric restriction has additive effects over caloric restriction alone on circulating adiponectin concentrations and adiponectin release from abdominal and gluteal adipose tissue. **Methods**: Overweight or obese (body mass index, 25–40 $kg \cdot m^{-2}$; waist >88 cm) postmenopausal women were randomized to 20-wk caloric restriction with and without aerobic exercise (CR + EX, $n = 48$; and CR, $n = 22$). Blood samples were collected for measuring plasma adiponectin concentration, and abdominal and gluteal subcutaneous adipose tissue biopsies were performed in a subgroup to determine *in vitro* adiponectin release, before and after the interventions. **Results**: The interventions elicited similar amounts of weight loss (CR + EX, −11.3 ± 4.6 kg; CR,−11.2 ± 3.4 kg) and fat loss (CR + EX, −8.0 ± 3.5 kg; CR, −7.4 ± 2.7 kg). The two groups had differential changes in plasma adiponectin concentrations (for interaction, $P = 0.014$); CR + EX increased (6.9 ± 3.9 to 8.5 ± 4.9 $\mu g \cdot mL^{-1}$; $P = 0.0001$), whereas CR did not alter (6.4 ± 4.4 to 6.5 ± 4.5 $\mu g \cdot mL^{-1}$; $P = 0.42$) plasma adiponectin. Likewise, adiponectin release from abdominal and gluteal subcutaneous adipose tissue increased with CR + EX ($P = 0.0076$ and $P = 0.089$, respectively) but did not change with CR ($P = 0.13$ and $P = 0.95$, respectively). **Conclusion**: Despite similar reductions in body weight and fat mass, the addition of aerobic exercise to caloric restriction increased plasma adiponectin concentrations, which may be partly explained by increased adiponectin release from abdominal and gluteal subcutaneous adipose tissue. **Key Words:** ADIPONECTIN, AEROBIC EXERCISE, CALORIC RESTRICTION, WEIGHT LOSS, POSTMENOPAUSAL WOMEN

APPLIED SCIENCES

Adipose tissue is an endocrine organ (20) that produces many factors, among which, adiponectin is a protein that is involved in energy metabolism, is anti-inflammatory, and plays a protective role in the development of atherosclerosis (23). Therefore, higher adiponectin concentrations may be associated with lower risks for cardiometabolic diseases. Although adiponectin is primarily produced by adipose tissue, obese individuals have lower circulating concentrations than lean people (5). Lifestyle interventions are commonly recommended for treating obesity (25). However, weight loss, induced by caloric restriction (CR) alone or the combination of caloric restriction and exercise (CR + EX), has shown inconsistent effects on circulating adiponectin concentrations; it is increased after weight loss in some studies (1–3,8,10,12,16–18,37) but not in others (6,28,35,37). These results do not always support that adiponectin concentration increases with certain amount of weight loss. Thus, there is still confusion regarding the effects of weight loss induced by CR + EX on adiponectin concentrations, and it is not clear about their interplay on adiponectin. Additionally, only a few studies have compared CR alone with CR + EX in the same study (1,10,17,35). Because of the potential role of adiponectin as a causal link between obesity and cardiometabolic diseases (13,15), it is of interest to clarify and to ascertain how CR + EX, the interventions that are commonly used in treating obesity, affect adiponectin.

Previous studies have shown changes in the size and number of adipocytes from abdominal and lower-body fat in response to overfeeding (38) and weight loss (39). However, only a few studies examined whether there are changes in adiponectin production by adipose tissue with weight loss, and the results are not conclusive. Therefore, the purposes of this study were to determine whether addition of aerobic exercise training to CR has additive effects, over CR alone, on circulating adiponectin concentrations, and to attempt to explain the inconsistent results from previous studies. Another purpose was to determine whether adiponectin release from subcutaneous adipose tissue

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changed in response to weight loss induced by CR alone and in combination with exercise.

METHODS

Participants. Participants in this study were a subset of those enrolled in a randomized clinical trial that was previously published (Clinicaltrials.gov identification: NCT00664729) (33). Briefly, participants completed 5 months of CR alone or combined with aerobic exercise (CR + EX). The participants were: (1) postmenopausal women between 50 and 70 yr, (2) overweight or obese (body mass index [BMI], 25–40 $kg \cdot m^{-2}$) and waist circumference >88 cm, (3) nonsmoking, (4) not on menopausal hormone therapy, and (5) sedentary (<15 min of exercise twice per week) in the past 6 months before enrollment. The study was approved by the Wake Forest University Institutional Review Board. All women signed an informed consent form to participate in the study according to the guidelines for human research.

Data used for the current analyses were from women who completed the 5-month intervention and had circulating adiponectin concentrations measured both at baseline and after intervention. There were 22 women in the CR-only group and 48 in the CR + EX group. Among these women, abdominal fat samples were obtained from 10 in the CR group and 15 in the CR + EX group, and gluteal fat samples were obtained from eight in the CR group and 13 in the CR + EX group, both at baseline and after intervention.

Interventions. The total energy deficits were designed to be approximately 2800 $kcal \cdot wk^{-1}$ for women in both the CR and CR + EX groups. Individual energy needs for weight maintenance were estimated based on each woman's resting metabolic rate and an activity factor based on self-reported daily activity (1.2–1.3 for sedentary individuals). The resting metabolic rate was determined via indirect calorimetry after an overnight fast by using a MedGraphics CCM/D metabolic cart and BREEZE 6.2 software (MedGraphics, St. Paul, MN). The energy deficits for the CR group resulted completely from reduction in dietary intake, whereas deficits for the CR + EX group resulted from the combination of reduction in dietary intake (~2100 $kcal \cdot wk^{-1}$) and exercise energy expenditure (~700 $kcal \cdot wk^{-1}$).

Throughout the 5-month interventions, all women were provided with daily lunch, dinner, and snacks prepared by the General Clinical Research Center (GCRC) metabolic kitchen. Women prepared their own breakfast meals from a provided menu plan. They were asked to eat only the food that was given to them or that from the breakfast menu. Energy make-up of the diet was approximately 25% from fat, 15% from protein, and 60% from carbohydrate. Women were allowed to consume noncaloric, noncaffeinated beverages *ad libitum*. All women were provided with daily calcium supplements (500 mg, two times per day). They were asked to keep a log of all foods consumed, and the records were monitored by dietitians to verify compliance.

The exercise intervention was center-based walking on treadmills three times per week under the supervision of an exercise physiologist. After flexibility exercise and walking for 3–5 min at a slow pace to warm up, women exercised at moderate or vigorous intensity (45%–50% to 70%–75% of heart rate reserve, which was the maximal heart rate, obtained from each woman's maximal exercise test described below, minus resting heart rate). The duration of the exercise was adjusted according to the intensity so that the estimated exercise energy expenditure was ~700 $kcal \cdot wk^{-1}$. Blood pressure was taken before and after each exercise session. Heart rate readings (by Polar heart rate monitor; Polar Electro Inc, Lake Success, NY) were taken before, at least two times during, and after the exercise.

Peak oxygen consumption. Peak oxygen consumption ($\dot{V}O_2$) was measured on a treadmill (Medical Graphics Corporation, Minneapolis, MN) during a progressive exercise test to voluntary exhaustion (33). The speed was set at a constant rate according to individual ability, and the incline increased at small intervals continuously throughout the test. A valid peak $\dot{V}O_2$ was obtained when at least two of the following criteria were met: (1) plateau in $\dot{V}O_2$ with increasing work rate, (2) maximal heart rate >90% of age-predicted maximal heart rate, and (3) respiratory exchange ratio of 1.1 or greater.

Body composition and fat distribution. Height and weight were measured with shoes and outer garments removed. Whole-body fat mass, lean mass, and percentage body fat were measured by dual-energy x-ray absorptiometry (Hologic Delphi QDR, Bedford, MA).

Adiponectin circulating concentrations and adipose tissue release. Blood samples were collected in EDTA-treated evacuated tubes by venipuncture in the early morning after an overnight fast before and after the interventions. The postintervention samples were collected at least 2 d after the previous bout of exercise. Plasma was separated and stored at −80°C until analysis. Plasma adiponectin concentration was measured by enzyme-linked immunosorbent assay using Quantikine kits (R&D System, Minneapolis, MN). The sensitivity for this assay was 0.2 $ng \cdot mL^{-1}$. The interassay and intra-assay coefficients of variation were 5.7% and 3.4% in our laboratory.

Abdominal and gluteal subcutaneous adipose tissue samples were taken via aspiration with a 16-gauge needle under local anesthesia after an overnight fast. The tissue was put in warm saline and transported immediately to the laboratory to be washed with warm saline to eliminate blood and connective tissue. Minced adipose tissue fragments (5–10 mg each, total of 200 mg) were placed in 2-mL medium 199 (Invitrogen, Carlsbad, CA) containing 1% bovine serum albumin (Serologicals, Norcross, GA), pH 7.4, and incubated in a shaking water bath at 50 rpm at 37°C under an atmosphere of 95% O_2 / 5% CO_2 for 3 h. At the end of the incubation, samples of the incubation medium were frozen at −80°C until final analysis. Adiponectin released from the adipose tissue was measured using aliquots of the

TABLE 1. Physical characteristics and body composition at baseline and after intervention by intervention group.

	CR (n = 22)	CR + EX (n = 48)
Age, yr	58.5 ± 6.1	58.4 ± 5.2
Race-ethnicity, n (%)		
Non-Hispanic white	13 (59.1)	34 (70.8)
African American	9 (40.9)	14 (29.2)
Height, cm	163.7 ± 5.8	164.1 ± 5.3
Weight, kg		
Baseline	89.8 ± 9.8	88.8 ± 11.7
Postintervention	78.6 ± 9.7	77.5 ± 10.9
BMI, $kg \cdot m^{-2}$		
Baseline	33.5 ± 3.8	32.9 ± 3.7
Postintervention	29.3 ± 3.6	28.7 ± 3.5
Total lean mass, kg*		
Baseline	53.3 ± 4.7	52.3 ± 6.0
After intervention	48.9 ± 5.1	48.9 ± 5.9
Total fat mass, kg		
Baseline	38.5 ± 6.7	38.4 ± 6.9
After intervention	31.1 ± 6.7	30.4 ± 6.4
Body fat, %		
Baseline	41.7 ± 3.9	42.2 ± 2.9
After intervention	38.5 ± 4.7	38.1 ± 3.9
Relative $\dot{V}O_{2peak}$, $mL \cdot kg^{-1} \cdot min^{-1}$**		
Baseline	20.9 ± 3.1	20.7 ± 3.3
After intervention	22.4 ± 4.6	23.7 ± 2.9

All data are mean ± SD.
No significant differences were observed between CR and CR + EX at baseline. Similar decreases between CR and CR + EX in body weight, BMI, fat mass, and body fat percent.
*P = 0.026 for group–time interaction, indicating significant difference in magnitude of changes between CR and CR + EX after interventions.
**P = 0.038 for group–time interaction, indicating significant difference in magnitude of changes between CR and CR + EX after interventions.
CR, caloric restriction; CR + EX, caloric restriction and exercise

incubation medium using an immunoassay (Millipore, St. Charles, MO).

Statistics. All analyses were conducted using the SAS software, version 9.3 (SAS Institute, Cary, NC). Descriptive statistics for normally distributed variables are presented as mean ± SD, median (quartiles) for non-normally distributed variables, or frequency in percentage. Natural logarithm was used to transform concentrations of adiponectin at baseline and after intervention to achieve normality of distribution. Analysis of variance with repeated measures was used to determine differences between the groups, changes after intervention (time), and interaction of the two factors. When the group–time interaction was significant, the main effect of time (changes after intervention) was examined in each group separately. An α level of $P = 0.05$ was selected to denote statistical significance.

RESULTS

Physical characteristics and body composition measurements of participants at baseline and after intervention are included in Table 1. Women in the CR and the CR + EX groups were of similar age, racial distribution, and height. There were no group differences in body weight, BMI, total lean mass, fat mass, body fat percent, or relative peak $\dot{V}O_2$ at baseline. Both interventions decreased body weight (12.5% ± 3.7% and 12.7% ± 4.7% for CR and CR + EX, respectively), BMI, fat mass (19.6% ± 7.0% and 21.0% ± 8.4%, respectively), body fat percent, by similar magnitude (for group–time interactions, $P > 0.10$ for all). There was a significant group–time interaction for total lean mass, which decreased in both groups ($P < 0.0001$ for both), and the decrease was slightly greater in the CR group (4.4 ± 1.8 kg) than in the CR + EX group (3.3 ± 1.8 kg) (P = 0.026). There were significantly different changes in peak $\dot{V}O_2$ relative to body weight (for group–time interaction, P = 0.038), with a greater increase in CR + EX (3.0 ± 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$; $P < 0.0001$) compared to CR (1.5 ± 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$; $P = 0.025$).

The mean concentration of circulating adiponectin was similar at baseline between CR (5.3 [2.8, 9.6] $\mu g \cdot mL^{-1}$, median [quartile 1, quartile 3] and CR + EX [6.4 (3.9, 9.6] $\mu g \cdot mL^{-1}$) groups (P = 0.47). However, changes with intervention were different between the groups (for group–time interaction, P = 0.014), with the concentrations significantly increased by 34% (P = 0.0001) with CR + EX (7.6 [4.4, 11.3] $\mu g \cdot mL^{-1}$ after the intervention) but unchanged (P = 0.42) with CR alone (5.2 [3.2, 8.9] $\mu g \cdot mL^{-1}$ after the intervention). Reports in the literature suggest the increase in adiponectin concentration occurs approximately 10% weight loss (see the "Discussion" section). Therefore, we further examined plasma adiponectin concentrations in those who have lost greater and less than the mean percentage of weight loss (12.7% ± 4.4%; Table 2). In the CR group, in those who lost more than 12.7% of weight, there was a trend for an increase in adiponectin concentration (P = 0.085). In contrast, in those in the CR group whose weight loss was less than 12.7%, adiponectin concentration did not change (P = 0.96). In the CR + EX group, adiponection concentrations increased in women who lost more than 12.7% (P = 0.002) and less than 12.7% (P = 0.007).

In the subgroup where abdominal and gluteal subcutaneous fat tissue samples were collected, baseline adiponectin release from abdominal fat was lower (P = 0.0025) in the CR (56.9 ± 24.1 $\mu g \cdot mL^{-1}$) than the CR + EX group (76.6 ± 22.0 $\mu g \cdot mL^{-1}$), but adiponectin release from gluteal fat was similar (76.0 ± 24.2 and 76.6 ± 19.7 $\mu g \cdot mL^{-1}$ for CR and CR + EX, respectively; P = 0.37) between the two groups.

TABLE 2. Plasma adiponectin concentrations at baseline and after intervention by intervention group.

	CR			CR + EX		
Group	All	Weight Loss >12.7%	Weight Loss <12.7%	All	Weight Loss >12.7%	Weight Loss <12.7%
Adiponectin, $\mu g \cdot mL^{-1}$	(n = 22)	(n = 10)	(n = 12)	(n = 48)	(n = 28)	(n = 20)
Baseline	5.3 (2.8, 9.7)	3.5 (2.6, 5.6)	8.4 (3.2, 10.9)	6.4 (3.9, 9.0)	7.0 (3.5, 12.3)	5.3 (3.9, 7.4)
After intervention	5.2 (3.0, 9.0)	4.0 (2.5, 5.8)	7.0 (3.4, 9.7)	7.6 (4.4, 11.4)	9.1 (5.6, 12.8)	6.4 (3.6, 10.0)
P value*	0.42	0.085	0.96	<0.001	0.002	0.007

Data are median (quartiles).
*Paired t-test on log-transformed data comparing baseline and after intervention.

After the interventions, adiponectin release from abdominal fat significantly increased in the CR + EX group (P = 0.0076) but did not change (P = 0.13) in the CR group (Fig. 1A). Adiponectin release from gluteal fat showed a trend to increase (P = 0.089) in the CR + EX group but did not change (P = 0.95) in the CR group (Fig. 1B). At baseline, there was significant association between adiponectin concentration and release from abdominal and gluteal fat (Spearman correlation: r = 0.43, P = 0.032; and r = 0.50, P = 0.021, respectively); however, the changes in adiponectin concentration and release from abdominal and gluteal fat were not significant in either group (P > 0.05 for all).

DISCUSSION

The primary finding of this study was that in postmenopausal women, with similar amount of weight loss (~12%), circulating adiponectin concentrations did not change with CR alone, but they significantly increased when the CR intervention was combined with aerobic exercise training. The changes in adiponectin release from subcutaneous adipose tissue support this in that the amount released from abdominal fat significantly increased and, from gluteal fat, showed a trend to increase, in the CR + EX group; whereas in the CR group, adiponectin release from both abdominal and gluteal fat was unchanged. Although the changes in adiponectin concentration and adipose tissue release were not associated, the changes were in the same direction after the CR + EX intervention. Therefore, the different changes in adiponectin release from subcutaneous fat in response to CR and CR + EX interventions may partly explain the different changes in circulating concentrations.

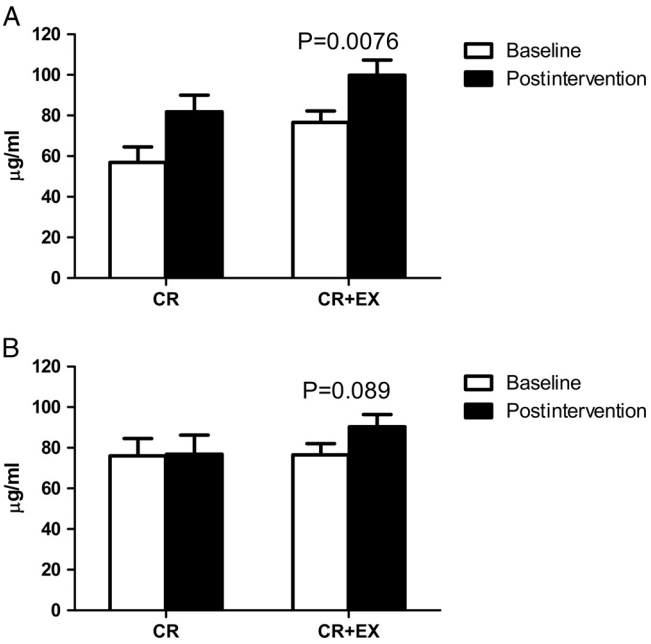

FIGURE 1—Adiponectin release from abdominal subcutaneous adipose tissue (A) and gluteal subcutaneous adipose tissue (B) before and after weight loss by intervention group (CR, caloric restriction; CR + EX, caloric restriction and exercise). Data are presented as mean ± SE. *P* values are for paired *t*-tests within the CR + EX group.

The lack of change in adiponectin concentrations in the CR group was somewhat surprising. Several previous studies examined adiponectin changes after CR interventions. Increased adiponectin concentrations have been reported in most (3,10,12,17,18,37) but not all studies (6,28,35,37). The findings of these prior studies support that weight loss close to 10% or more is associated with increased adiponectin concentrations. As an example, in one of these studies, adiponectin concentration did not change with 5% weight loss but increased with 10% weight loss (37). There may also be a sex difference, with men having a larger increase in adiponectin than women (3). In fact, the aforementioned studies that did not show an increase in adiponectin concentration were in women only (5%, 7.5%, and 7% weight loss) (6,35,37) or with women as most of the study sample (average of ~11% weight loss) (28). Differently, in studies that showed increased adiponectin concentration, either there was a significant percentage of both men and women (2,10,12,17) or there was a large amount of weight loss (>15%) when there were women only (18) or only a small percentage of women was included (8). In our study, the average 12.7% weight loss in the CR group did not increase adiponectin concentration. In women who lost more than 12.7% of weight showed a trend for increased adiponectin concentration, and those who lost less than 12.7% of weight did not show any change. Putting these study findings together, in women, an even larger weight loss may be needed by CR to induce changes in circulating adiponectin concentration. We suspect that this may be due to the greater percent body fat in women than men; as a result, similar amount of total weight loss is often associated with smaller percentage of fat mass loss in women, and adiponectin is primarily produced by adipose tissue.

As we discussed earlier, we concluded that in women, a larger amount of weight loss may be needed to increase adiponectin concentration, where weight loss was induced by CR only. In line with this, in our study, 12.7% weight loss induced by CR alone did not result in any change in adiponectin. Yet, an increase was observed in those with the addition of exercise with the same amount of weight loss. In fact, for women in CR + EX, adiponectin concentrations increased no matter whether they lost less or greater than the average weight loss of 12.7%. Therefore, exercise may "sensitize" the adiponectin response to weight loss because it seems that the same amount of weight loss increased adiponectin concentration in women with exercise added to the CR intervention, whereas CR alone did not increase adiponectin.

The effects of exercise alone on adiponectin concentration are also inconsistent. Most studies do not show a change in adiponectin concentration with exercise training (1,10,16,17,24,34). On the contrary, other studies showed that exercise training increased adiponectin despite unchanged body weight (29) or very small weight loss (32). Similar to CR-induced weight loss, these two studies were in men only,

and those that did not show a change in adiponectin concentration included a mixed sample of men and women (10,16,17,24) or women only (1,34). Among these studies, the timing of adiponectin measurement was reported as at least 24 h after the last exercise bout in a few (16,17,24), but the timing was not reported in others. Therefore, we cannot rule out the possibility that the inconsistency of timing in relation to the last exercise contributes to the inconsistent findings.

Only a few studies examined the effects of CR + EX on adipose tissue adiponectin production. Weight loss via CR seems to increase subcutaneous abdominal adipose mRNA expression of adiponectin (11,17,36). However, inconsistent results regarding exercise alone have been reported. One study found 3.5% weight loss induced by aerobic exercise three times per week, with an estimated energy expenditure of 500–600 kcal per session in a mixed sample of men and women, with increased abdominal subcutaneous adipose tissue adiponectin mRNA expression (17). Another study, however, showed unchanged abdominal adipose adiponectin mRNA in women after 12-wk aerobic exercise five times per week of 45 min at 50% of maximum $\dot{V}O_2$, although there was an average 5.9% of weight loss (34). Strength training did not change abdominal adipose tissue adiponectin mRNA either (27). As with CR alone, weight loss by exercise combined with CR seems to increase abdominal adipose tissue mRNA expression of adiponectin (11,16,17). Gene expression levels may not always be reflected in protein levels. There is also evidence of culture of human adipose tissue showing alteration in mRNA gene expression (21). Our study was unique because we examined the *in vitro* adiponectin release from subcutaneous adipose tissue in two fat depots. Our findings support that exercise sensitizes the response of adiponectin to a weight loss intervention. In addition, we are not aware of any studies involving CR or exercise interventions that have conducted gluteal subcutaneous adipose tissue biopsy. Our study suggests that changes in adiponectin release from gluteal fat were in the same direction as that from abdominal fat, but of less magnitude. We recognize that the adiponectin release method we used is limited to the tissue collected from the biopsy and that the bovine serum albumin that was used in the media may influence experimental outcome, as it may contain growth factors (14). This method quantifies the amount of adiponectin released from the adipose tissue during the incubation period, which represents synthesis by adipocytes and other cells in the tissue. However, whether cells other than adipocytes contribute to circulating adiponectin in humans is still unanswered (19).

We did not have information regarding adiponectin production by other fat depots, such as deep subcutaneous adipose tissue or visceral fat. It has been shown that deep subcutaneous adipose tissue has different characteristics than subcutaneous adipose tissue (31) and that adiponectin mRNA expression is lower in visceral than subcutaneous adipose tissue (30). Despite our small sample size on adipose adiponectin release data, our findings regarding the different effects between the two interventions were consistent with previous findings of greater reduction in abdominal adipocyte size after CR + EX in comparison with CR only (39).

Exercise and CR–induced weight loss may function via different mechanisms to influence adiponectin concentration. One study showed that mRNA expression of adiponectin receptors 1 and 2 in skeletal muscle significantly increased in exercise-trained individuals but not in those undergoing a hypocaloric diet (17). Moreover, weight loss by CR seems to be associated with an increase in high–molecular weight (HMW) adiponectin (2,9). Regarding exercise alone, one study showed that irrespective of any associated weight loss, there was a shift in the adiponectin multimer distribution toward a lower molecular weight (LMW) (7); two other studies showed no changes in HMW adiponectin after exercise training (4,17); yet, another study showed that HMW adiponectin concentration increased (26). Thus, with current evidence, we cannot determine whether exercise training and CR–induced weight loss have different effects on adiponectin multimer complex composition. Unfortunately, we did not measure adiponectin multimer distribution in our study. Because high–molecular weight (HMW) adiponectin is more closely (negatively) associated with insulin resistance than total plasma adiponectin concentration (22), it is important to determine how adiponectin multimer distribution changes in response to interventions, and this may lend insight regarding the inconsistent findings from previous studies.

In summary, our study found that circulating adiponectin concentration did not change with weight loss by CR only but increased with the addition of aerobic exercise training. The changes in *in vitro* adiponectin release from subcutaneous abdominal and gluteal adipose tissue were in line with changes in circulating adiponectin concentration. Our data and others support that in women, a greater percentage of weight loss may be needed to increase adiponectin concentration than men and that exercise strengthens the effects of weight loss on adiponectin.

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The authors have nothing to disclose.

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Clinical Trial Registration: Clinicaltrials.gov identification: NCT00664729.

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