

PAPER

Is serum leptin related to physical function and is it modifiable through weight loss and exercise in older adults with knee osteoarthritis?

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OBJECTIVE: To determine the effect of weight loss and exercise interventions on serum leptin and to investigate the relationship of physical function and osteoarthritis (OA) severity with serum leptin in older overweight and obese adults with knee OA. In addition, the study examined if serum leptin predicts weight loss.

DESIGN: Longitudinal, controlled clinical trial of weight loss and exercise interventions.

SUBJECTS: Community dwelling, older, overweight and obese adults ($n=316$; >60 years of age; body mass index $\geq 28.0 \text{ kg m}^{-2}$) with symptomatic knee OA and self-reported difficulty in performing selected physical activities were recruited.

INTERVENTIONS: Participants were randomized into one of four groups for the 18-month study duration: Healthy Lifestyle Controls, Dietary Weight Loss (Diet), Exercise Training (Exercise), and a combination of Dietary Weight Loss and Exercise Training (Diet + Exercise). The weight loss goal for the two Diet groups was 5% from baseline at 18 months. Participants in the Exercise groups were trained for 3 days week⁻¹, 60 min day⁻¹.

MEASUREMENTS: Body weight, body mass index, serum leptin, physical function, and OA severity were measured at baseline, 6 months, and 18 months.

RESULTS: Diet and Diet + Exercise groups lost 5.3 and 6.1% of their weight, respectively, at 18 months with the Exercise group losing 2.9%. There was a significant main effect of weight loss on serum leptin with a decrease in serum leptin averaged across the 6- and 18-month time points for the Diet and Diet + Exercise groups compared to the other two groups ($\beta=0.245$; $P<0.01$). No main effect for exercise training was observed. Serum leptin was related to self-reported physical function. In all participants, a mixed model analysis demonstrated that lower levels of baseline serum leptin predict larger weight loss ($\beta=-2.779$; $P=0.048$).

CONCLUSION: Decreases in serum leptin may be one mechanism by which weight loss improves physical function and symptoms in OA patients.

International Journal of Obesity (2004) 28, 1383–1390. doi:10.1038/sj.ijo.0802737

Published online 27 July 2004

Keywords: lifestyle behavior intervention; obesity; overweight; disability

Introduction

The study of obesity has progressed dramatically since 1994 with the discovery of the ob gene product leptin.¹ Produced primarily by white adipose tissue, this protein is involved in energy regulation at the level of the hypothalamus² through modification of energy intake and energy expenditure via a

negative feedback loop.³ Since leptin is primarily synthesized in adipocytes, there is a strong relationship between circulating leptin levels and indices of body fat.^{4–6} This correlation remains in older adults,⁷ but appears to be weaker with aging.⁸ Short-term weight loss decreases circulating concentrations of leptin such that an individual at a reduced body weight has a lower blood leptin level than weight stable individuals at a similar body weight.^{6,9} Following acute weight loss, plasma leptin remains correlated with body fat, both in young and older individuals.^{6,7,10} However, the longer-term effects of weight loss (ie greater than 6 months) on serum leptin levels are not known.

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Received 5 November 2003; revised 7 May 2004; accepted 24 May 2004; published online 27 July 2004

Recent evidence suggests that leptin may act locally in joint tissues but its exact function is not clear.¹¹ Leptin receptors are found on chondrocytes, and leptin stimulates cell proliferation in these isolated cells.¹² Moreover, leptin may be involved in the repair processes of OA through its anabolic action,¹¹ or in the induction/progression of the disease by working with interferon- γ to stimulate nitric oxide production in chondrocytes.¹³ There is also recent compelling evidence indicating leptin's presence in synovial fluid and in cartilage and osteophytes from individuals with OA, but not in cartilage from normal controls.¹⁴ Other adipocytokines, including resistin and adiponectin, have also been found in synovial fluid of patients with OA and rheumatoid arthritis, indicating a possible role for adipose tissue serving as a metabolic modulator of arthritic conditions.¹⁵

Recent data show that leptin is present in the synovial fluid from subjects with OA and rheumatoid arthritis,¹⁶ and this hormone is made locally by joint tissues.¹⁴ We speculate that leptin may provide a metabolic link between obesity and OA,¹¹ as leptin has been shown to increase synthesis of transgenic growth factor β (TGF β), a known stimulator of osteophyte formation.¹⁷ Several investigations have shown that inflammatory biomarkers are associated with declines in physical function, as reported with physical performance tasks and self-reported disability.^{18–21}

Lifestyle changes to promote weight loss and increase physical activity levels are typically prescribed as initial treatment for obese individuals with osteoarthritis. Given that the prevalence of obesity and osteoarthritis is on the rise in the older adult population,^{22–24} and that leptin metabolism is altered in obesity and osteoarthritis, it is relevant to evaluate the long-term impact of weight loss and exercise interventions on serum leptin levels in OA patients. Owing to leptin's role in chondrocyte and osteophyte metabolism, changes in leptin concentrations may be one mechanism by which both dietary weight loss and exercise training interventions improve pain and physical function in older adults with knee OA.^{25–27}

Based on leptin's actions on energy balance, it is reasonable to speculate that the hormone plays a role in predicting weight change in a population, although results from previous studies in this area are conflicting. For example, in young nondiabetic, Pima Indians, those that gained weight over a 3-year period, had lower plasma leptin levels at baseline than those who maintained their weight.²⁸ This indicates a relative deficiency of a satiety signal from adipose tissue. In contrast, other studies in obese children and young men and women show that low plasma leptin levels are predictive of weight loss, suggesting a greater sensitivity to circulating serum leptin.^{29–32} Identifying biological predictors of weight loss may aid in devising interventions that directly affect biomarkers and provide success in weight management for OA patients.

Specifically, the primary aim of the present study was to investigate changes in serum leptin levels following 18 months of dietary weight loss and exercise training in older

overweight and obese adults with OA of the knee. Secondly, the relationships between serum leptin and measures of physical function and OA X-ray scores were performed in this population. The investigation also examined if serum leptin levels at baseline predicted subsequent weight loss. It was hypothesized that the dietary weight loss intervention would reduce plasma leptin levels, and that leptin would be related to measures of physical function.

Methods

Participants

Study participants were enrolled in the Arthritis, Diet, and Activity Promotion Trial (ADAPT). Complete details of this study design and primary outcome measures are found elsewhere.³³ The primary aim of ADAPT was to compare the effects of an 18-month dietary weight loss intervention (Diet), an exercise intervention (Exercise), a combined exercise–dietary weight loss intervention (Exercise–Diet), and a healthy lifestyle control group (HL) on self-reported disability and physical function in older, overweight and obese, sedentary adults with knee OA. Briefly, 316 community dwelling older adults (>60 years of age) with symptomatic knee OA were recruited. Additional inclusion criteria included a body mass index (BMI) $\geq 28.0 \text{ kg m}^{-2}$, a sedentary lifestyle, and self-reported difficulty in performing at least one of the following activities attributed to knee pain: lift and carrying groceries, walking one-quarter mile, getting in and out of a chair, or going up and down stairs.

Study design

Both Diet and Exercise–Diet groups were prescribed similar dietary weight-loss intervention strategies. The weight loss goal for these two groups was a mean loss of $\geq 5\%$ of initial body weight. Both group and individual diet sessions were utilized throughout the duration of the investigation in a 3:1 ratio with one in every four sessions being an individual appointment. The first 4 months were termed the intensive phase with weekly meetings conducted by a registered dietitian trained in the intervention strategy. The topics in the intensive phase focused on healthful food selection with portion and dietary fat control to decrease energy intake, emphasizing an increased awareness in the consequence of and the need to change dietary habits. Participants were individually counseled on reducing energy intake by $\sim 250\text{--}500 \text{ cal day}^{-1}$ to achieve the desired weight loss. Biweekly meetings were held during months 5 and 6 of the transition period. During the maintenance period of months 7–18, diet meetings were held monthly. In addition to these meetings, phone contacts were alternated every 2 weeks to provide interventionist–participant contact on a biweekly basis. Further contact was conducted through newsletters distributed regularly that provided pertinent nutrition information and a schedule of events for the intervention groups. The goals of the maintenance phase included assisting in weight maintenance for those that had achieved their weight

loss goals, and to provide counsel for participants who had a difficult time in losing weight and adhering to the intervention.

The exercise program was conducted 3 days week⁻¹ for 60 min session⁻¹ and was similar for the Exercise and Exercise–Diet groups. Participants were engaged in a structured, facility-based training program for the first 4 months of the intervention and then had the option to transition to a home-based program or to continue exercising in the facility. The exercise program consisted of a warm-up phase (5 min), an aerobic phase (15 min), a strength phase (20 min), a second aerobic phase (15 min), and a cool-down phase (5 min). The primary mode of aerobic training consisted of walking. The exercise intensity for the aerobic exercise was 50–85% of the heart rate reserve using the symptom limited maximum heart rate obtained from a graded exercise test (GXT). Strength training included four stations: leg extension, leg curl, heel raise, and step-ups using ankle cuff weights and a weighted vest. Two sets of 12 repetitions were performed at each station. Resistance was progressively increased during the intervention as strength improved. Lower-body flexibility exercises were also performed at each session. Weights were provided to the participants if they chose to perform home-based exercises.

Participants randomized to the HL group met monthly for 1 h during the first 3 months of the trial. Topics for these sessions included OA, obesity, and exercise. In addition, phone contacts were performed on a monthly (for months 4–6) and bimonthly (months 7–18) basis.

Measurements

Descriptions and time course of all measurements obtained in ADAPT are reported elsewhere.³³ Only the variables analyzed in this report will be discussed in detail here. Demographic information was obtained from all participants in ADAPT prior to the initiation of the intervention. At baseline, 6 months, and 18 months, participants reported to the General Clinical Research Center (GCRC) of Wake Forest University Medical Center after a 12-h overnight fast. At this time, height and body weight were determined for calculation of BMI and a fasting blood sample was drawn via venipuncture. Serum concentrations of leptin were determined by enzyme-linked immunosorbent assay (ELISA) using a kit from R&D Systems, Minneapolis, MN, USA. All samples were measured in duplicate and the average of the two values was used for data analyses. Duplicate samples that did not provide a coefficient of variation of <15% were reanalyzed and all the values were averaged for data analysis.

Self-reported physical function, pain, and stiffness were measured using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC).³⁴ The WOMAC has been validated, and is recommended by the Osteoarthritis Research Society as the measure of choice.³⁴ The 24-item WOMAC instrument was developed for use by individuals

who have OA of the hip or knee and is a health status instrument that assesses participant's perception of pain, joint stiffness, and physical function. Physical performance was determined using the 6-min walk distance. Participants were instructed to walk as far as possible in a 6-min time period on an established course. They were not allowed to carry a watch and were not provided with feedback during the trial. The total distance covered was divided by the 6 min time period to provide walking speed.

Radiographic severity of OA was assessed through anteroposterior standing knee X-rays using a classification scheme adapted from Altman *et al*.³⁵ Both the medial and lateral compartments were graded for osteophytes, subchondral cysts, and joint space narrowing on a 0–3 Likert scale using an atlas. An overall mean for the combined medial and lateral compartments was determined and used in the analysis.

Statistical analysis

A repeated measures analysis of variance with a random effect for subject was used for the primary analysis. The change in the logarithm of serum leptin was the dependent variable and lifestyle intervention of weight loss and exercise and their interaction were the primary predictor variable. Additional covariates included visit (6 or 18 months), gender, race, and the levels of serum leptin, age, and BMI at baseline. In an additional model, we added longitudinal BMI to observe the relationship between serum leptin and BMI. The same covariates as above were also used in this latter model. Mixed model analysis of variance examined the relationship between plasma leptin and physical function and physical performance. A linear model (reported as β) was applied to assess the relationship between plasma leptin with both physical function and inflammatory biomarkers adjusted for age, gender, and BMI.

We also investigated serum leptin as a predictor for weight loss using a mixed model with weight loss as the dependent variable and baseline serum leptin as the predictive variable. We examined weight loss as the change in weight from baseline at 6 and 18 months. Baseline weight, lifestyle intervention, age, follow-up visit, gender, and race were included as covariates. Furthermore, in a subsequent analysis, the relationship between the main effects of diet and exercise and the row variables found in Table 1 was performed using Generalized Linear Modeling (GLM). Data are presented as mean (s.d.). All the performed analyses required records with complete data; records with missing data for any of the variables used in a particular analysis were omitted from that analysis.

Results

Descriptive statistics for the participants in each of the four arms of the study are presented in Table 1. There were no significant differences among the groups at baseline for age,

Table 1 Baseline characteristics and follow-up measures for body weight, BMI, and leptin

Mean (s.d.)	Healthy Lifestyle	Dietary Weight Loss	Exercise	Diet+Exercise	Diet main effect P-values	Exercise main effect P-values
Number	N=76	N=80	N=79	N=74	—	—
Age (y)	68.7 (6.2)	67.8 (5.5)	69.1 (6.5)	68.7 (6.7)	0.345	0.393
Gender (% female subjects)	67.1	71.3	75.9	74.3	0.800	0.243
Body weight at baseline (kg)	95.8 (18.9)	95.1 (15.2)	92.1 (14.6)	91.9 (17.3)	0.810	0.070
Body mass index at baseline (kg m ⁻²)	34.3 (5.0)	34.5 (4.9)	34.2 (4.8)	34.2 (5.6)	0.880	0.758
Weight loss (% from baseline)						
6 months	1.3	4.1	0.0	6.4	—	—
18 months	1.8	5.3	2.9	6.1	—	—
Leptin (ng ml ⁻¹)						
Baseline	34.3 (22.9)	34.7 (23.1)	31.7 (19.0)	33.5 (19.6)	0.641	0.443
6 months	38.7 (27.3)	26.1 (19.8)	32.0 (21.5)	26.4 (18.3)	—	—
18 months	30.6 (20.5)	26.1 (18.4)	29.9 (23.0)	30.4 (20.7)	—	—

Values are presented as means (s.d.) unless indicated. There were no significant interactions for the Diet and Exercise main effects. *N*'s represent the max participants within each grouping.

gender distribution, body weight, BMI, or serum leptin. As expected, there was a significant positive relationship between serum leptin and BMI ($\beta=0.118$; $P<0.01$). There was neither a significant age nor age by BMI interaction effect on the association between serum leptin and BMI when participants were dichotomized into <70 and >70 years. There was, however, a gender interaction for the BMI and serum leptin relationship ($P=0.035$).

Body weight and BMI were significantly lower at 6 and 18 months for the two weight loss groups (Diet and Exercise–Diet) compared to the Healthy Lifestyle Controls (Table 1). The Diet group lost 4.1% of their weight at 6 months, with a further decrease to 5.3% by 18 months. The Exercise–Diet group lost 6.4% at 6 months and 6.1% at 18 months. In contrast, the controls lost less than 2% of their body weight by 18 months and the Exercise group only dropped 2.9% by 18 months.

There was a significant main effect of the dietary weight loss intervention on serum leptin with a decrease in serum leptin averaged across the 6 and 18 month time points occurring for the Diet and Exercise–Diet groups compared to the other two groups ($\beta=0.245$; $P<0.01$) (Figure 1). This was apparent following adjustment for baseline BMI values. However, the exercise intervention showed no main effect on leptin levels. Additionally, there was no interaction between exercise and dietary weight loss on changes in serum leptin. In a further analysis of the data, we observed a weight loss by gender interaction on the change in leptin concentrations with female subjects demonstrating a greater decrease in leptin than male subjects ($P=0.043$).

Severity of OA as derived from radiographs was determined at baseline and 18 months. The overall mean score was 2.25 (0.82) at baseline, and 2.39 (0.81) at 18 months. There was no significant correlation between plasma leptin levels and these scores ($r=0.044$; $P=0.521$, baseline; $r=0.057$; $P=0.408$, 18 months). This finding was also apparent when examining the change across the time points in the two variables ($r=-0.053$; $P=0.461$) and in a partial

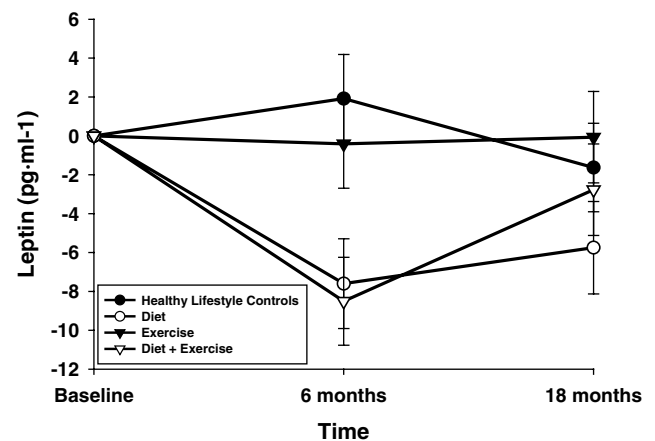


Figure 1 Group changes in serum leptin. Mean values (s.d.) for the change at each time plot are plotted across time for each of the four intervention arms. A significant main effect for diet was observed, but not for exercise.

correlation for change in plasma leptin and OA scores ($r=-0.057$; $P=0.431$) using BMI as the covariate. However, in the analysis of functional indices of OA severity, there was a significant relationship between serum leptin and WOMAC function ($\beta=0.114$; $P=0.039$) and stiffness ($\beta=0.152$; $P=0.039$) subscales. This relationship was not apparent for serum leptin with 6 min walk distance or WOMAC pain. (See Table 2 for baseline values of these variables.)

Mixed modeling analysis showed that weight loss had a negative relationship with serum leptin at baseline ($\beta=-2.779$; $P=0.048$) across all participants (ie lower baseline leptin predicted greater weight loss). A significant relationship was also observed between the change in body weight and the change in leptin with a greater weight loss leading to a larger change in serum leptin ($\beta=0.047$; $P<0.001$) (Figure 2). A mixed model analysis examining baseline serum leptin as a predictor for weight loss is shown in Table 3. The covariates used in this model included type of intervention, baseline weight, age, follow-up visit, gender,

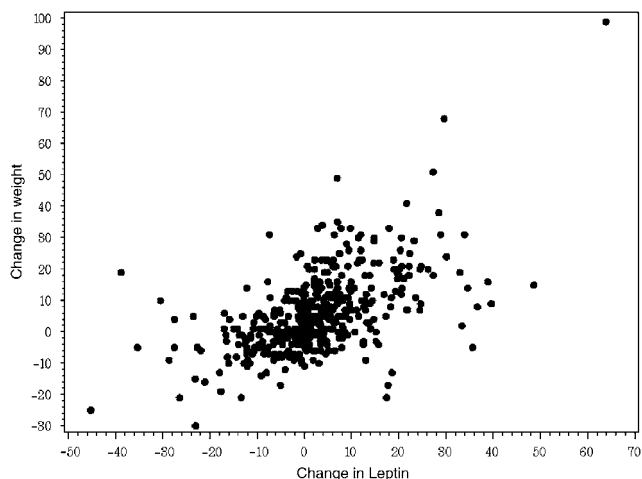


Figure 2 Relation between change in serum leptin and change in body weight. A significant relationship was observed among the two variables ($\beta = 0.047$; $P < 0.001$).

Table 2 Walking speed during the 6 min walk and self-reported physical function at baseline

Variable	Concentration (s.d.)
Walking speed (m s^{-1})	1.18 (0.22)
WOMAC function (units)	1.39 (0.69)
WOMAC pain (units)	1.82 (0.74)
WOMAC stiffness (units)	1.34 (0.68)

Values are presented as means (s.d.)

and race. Results suggest that lower levels of baseline serum leptin predict larger weight loss. As shown in the table, other significant predictors for weight loss include race and gender. A negative weight loss is indicative of a weight gain. An example of the prediction equation is as follows: A 70-y-old African-American male at the 6 month visit who was 110 kg at baseline, had a leptin of 33.6, and was not on diet or exercise (ie in the control group); he would have an estimated weight gain of 4.82 kg (see equation below): $-2.09 + 0.21 \times 110 - 2.78 \times \log_e(33.6) + 0 - 8.66 - 0.27 + 0.06 \times 70 - 6.87 - 4.46 = -4.82$ kg, which actually means there would be an increase of 4.82 kg from baseline at the 6-month visit. Conversely, if that person was female and in the dietary intervention, then there would be an estimated weight loss of 10.71 kg (see equation below): $-2.09 + 0.21 \times 110 - 2.78 \times \log_e(33.6) + 0 - 0 - 0.27 + 0.06 \times 70 - 0 - 4.46 = 10.71$ kg.

Discussion

The understanding of leptin's role in various biological processes has evolved since the isolation of the hormone a decade ago. It no longer is thought exclusively as a satiety

Table 3 Leptin as predictor for weight loss using mixed model analysis

Effect	Estimate	Standard error	P-value
Intercept	-2.09	10.90	0.848
Baseline weight	0.21	0.06	<0.001
Baseline logA	-2.78	1.40	0.048
Leptin			
Visit			
18 months	1.28	0.79	—
6 months	0	—	0.106
Diet intervention			
= No	-8.66	1.32	—
= Yes	0	—	<0.001
Exercise intervention			
= No	-0.27	1.34	—
= Yes	0	—	0.843
Age	0.06	0.12	0.606
Gender			
= 1 (males)	-6.87	2.64	—
= 2 (females)	0	—	0.010
Race			
Black	-4.46	1.64	—
Other	-5.05	5.02	—
White	0	—	0.019

Covariates include intervention type, baseline weight, age, follow-up visit, gender, and race.

hormone, but it is now known to affect more than energy balance, including immune response, inflammation, and cell proliferation.^{12,36-39} Ultimately, altering circulating leptin levels through interventions may affect the regulation of physiological processes that may be involved in comorbidities associated with obesity. As we have shown in an earlier analysis, dietary weight loss intervention improved self-reported physical function; therefore, the current study investigated whether serum leptin is affected by the interventions in the study. Furthermore, the study examined the relationship between leptin and indices of physical function and OA severity in radiographs. It was thought that if the intervention decreases serum leptin, this may be one mechanism by which weight loss improves physical function and symptoms in OA patients. Hence, it is critical to understand the response in circulating leptin levels from weight loss and exercise training, especially in disease states such as OA, in which leptin may be causally involved. Findings from our study add to existing knowledge about the effects of a dietary weight loss intervention by showing that a longer-term intervention also decreases circulating leptin. The novelty of this study is that we examined leptin changes from weight loss and exercise training in an older obese adult population with knee OA.

Circulating concentrations of leptin are influenced by the quantity of adipose tissue in the body,^{4,7} and administration of the hormone to leptin-deficient animal models decreases body weight through lowering food intake and raising energy expenditure.⁴⁰ These studies demonstrate that leptin is involved in the regulation of body energy balance.^{30,41} Recent evidence hints that leptin may be involved in certain disease states. Levels of this hormone are elevated in synovial

fluid in patients with OA compared to normal controls.¹⁴ Dumond *et al* did not measure plasma levels of leptin and we did not determine synovial levels of leptin, thereby making a comparison difficult. However, in patients with rheumatoid arthritis, leptin levels were correlated in plasma and synovial fluid and those with rheumatoid arthritis had higher concentrations of leptin than control samples. Currently, the relationship between leptin levels in serum/plasma and synovial fluid has not been examined in patients with OA.

There is a strong relationship with obesity and OA, as obesity is a risk factor for OA in the knee as well as the hands and hips.^{42–44} The current results provide further support that leptin may have a role in OA as a significant relationship was observed in self-reported physical function and stiffness measures with the hormone. Higher leptin concentrations were related to greater impairments in self-reported measures of physical function. In contrast, there was no relationship between serum leptin and radiograph scores of OA severity.

Clinical experience and previous research strongly support the incorporation of both dietary and exercise modifications in successful weight management programs. The factorial design of the present study allowed examination of the main effects of these two interventions along with their interaction on serum leptin levels. The results indicate that serum leptin is reduced by a long-term diet (weight loss) intervention. These significant changes in serum leptin were seen even though the weight loss was modest (5–6%). Interestingly, at the 6-month time point, there was a 21.2 and a 24.7% decrease in serum leptin levels in Dietary Weight Loss and Exercise + Dietary Weight Loss groups, respectively. However, the change in serum leptin from baseline was equal or less at 18 months than 6 months (24.7 and 9.5% at 18 months for Dietary Weight Loss and Exercise + Dietary Weight Loss, respectively), although weight loss was greater at the latter time point for the Dietary Weight Loss group. The nearly 25% drop in leptin observed at 6 months was considerably less than the 50% decrease reported by others, although this may be related to the greater weight loss observed in those studies.^{30,45–47} For example, a very low calorie diet (800 kcal day⁻¹) over a 10-week period produced a 13.6% decrease in body weight with a 50% drop in serum leptin levels.⁴⁸ These participants were nearly 20 years younger and much heavier than those in the current study with an average BMI of 50 kg m⁻².

Consistent with the previous literature, the exercise training program in ADAPT had no independent effect on serum leptin concentrations.⁴⁹ Others have shown that exercise influences plasma leptin levels independent of weight loss.^{5,50} The intensity and volume of the training, and total energy expended, may influence this effect, as we previously showed that different levels of exercise have differing effects on the acute response from the exercise bout.⁵ It would be expected that intensity and total volume of exercise would be less in older adults utilized in the study

compared to younger cohorts. Alternatively, it could be postulated that the signaling for the expression of leptin may be less sensitive to the changes in the hormonal and energy-yielding substrates when they are caused by an exercise program vs dietary energy restriction.

The hyperleptinemia that is commonly present in obese humans suggests that there is a defect in the recognition of the hormone by the receptor in the hypothalamus, and not in a deficiency of leptin production by the adipocytes. This implies a leptin resistance similar to the insulin resistance in type II diabetes.^{51,52} It is not certain if the leptin resistance present in the hypothalamus is a cause or a consequence of obesity. It is also not clear if leptin resistance might occur in joint tissues where recent work has shown that leptin could have a physiological role. Leptin receptors are present in cartilage and if leptin is shown to be an anabolic factor, as suggested by its ability to stimulate IGF-I and TGF- β production, then leptin resistance could be detrimental to cartilage homeostasis. On the other hand, if leptin sensitivity is normal but leptin stimulates osteophyte formation through production of TGF- β , then elevated leptin levels associated with obesity may provide a metabolic link between fat mass and changes in joint tissues seen in OA.¹¹ Further research on leptin's role in cartilage metabolism is necessary to fully understand the consequences of hyperleptinemia and decreases in leptin with weight loss in patients with OA.

We also found that initial baseline leptin levels were a predictor for subsequent weight loss, with lower baseline levels of leptin predicting greater weight loss, even after adjusting for baseline body weight, intervention arm, age, gender, and race. This finding is also consistent with leptin resistance being a potential contributor to obesity and hinders weight loss. Lower leptin concentrations may indicate that the leptin receptor is more sensitive to the available leptin, thereby producing the desirable weight loss effect. Our data support the notion that the lower leptin levels signify an enhanced leptin sensitivity, which produced a greater weight loss during a period of negative energy balance. Verdich also showed that leptin was inversely related to weight loss in 28–39-year old men, indicating that an increase in leptin sensitivity was associated with greater weight loss.³⁰ Moreover, in a prospective analysis of the Health Professionals Follow-Up Study of overweight men, weight gain over 4 years was associated with a high leptin level.⁵³

In conclusion, the weight loss intervention utilized in this study produced significant changes in body weight and in leptin concentrations at the 6- and 18-month follow-up. In contrast to some existing studies, exercise alone did not affect leptin concentrations. In addition, low baseline leptin levels predicted greater weight loss over the 18-months of follow up. As the knowledge for leptin's role in cartilage metabolism advances, these findings may help in understanding the mechanism for weight loss effects on improvements in OA symptoms and physical function.

Acknowledgements

This project was funded by the Claude D Pepper Older Americans (Grant 5P60AG10484-00) and the General Clinical Research Center (Grant M01-RR07122).

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