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The Independent and Combined Effects of Physical Activity and Weight Loss on Inflammatory Biomarkers in Overweight and Obese Older Adults

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Abstract

Objectives—To determine the independent effect of long-term physical activity (PA) and the combined effects of long-term PA and weight loss (WL) on inflammation in overweight and obese older adults.

Design—18-month randomized, controlled trial.

Setting—This study was conducted within the community infrastructure of Cooperative Extension Centers.

Participants—288 older (60–79 years), overweight and obese (BMI > 28 kg/m²) community dwelling men and women at risk for cardiovascular disease (CVD).

Intervention—PA + WL (n=98), PA only (n=97), or successful aging (SA) health education (n=93) intervention.

Measurements—Biomarkers of inflammation (adiponectin, leptin, hsIL-6, IL-6sR, IL-8, and sTNFR1) were measured at baseline, 6 and 18 months.

Results—After adjustment for baseline biomarker, wave, gender and visit, both leptin and hsIL-6 showed a significant intervention effect. Specifically, leptin (ng/ml) was significantly lower in the PA+WL group compared to PA or SA [21.3 (95% CI: 19.7–22.9) vs. 29.3 (26.9–31.8) and 30.3 (27.9–32.8), respectively; both $p < 0.01$], and hsIL-6 (pg/mL) was also significantly lower in the

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PA+WL group compared to PA or SA [2.1 (95% CI: 1.9–2.3) vs. 2.5 (2.3–2.7) and 2.4 (2.2–2.6), respectively; both $p<0.05$].

Conclusion—Addition of dietary-induced WL to PA reduced leptin and hsIL-6 compared to PA alone and to a SA intervention in older adults at risk for CVD. Results suggest that WL, rather than increased PA, is the lifestyle factor primarily responsible for improvement in the inflammatory profile.

Keywords

physical activity; weight loss; inflammation; aging

INTRODUCTION

Chronic low-grade inflammation is associated with advanced age and adiposity, and predisposes individuals to several chronic conditions, including cardiovascular disease (CVD), diabetes, and physical disability.^{1,2} Thus, the inflammatory pathway is a potential therapeutic target for lifestyle interventions designed to reduce disease and disability in older adults. It is well recognized that regular exercise is an effective countermeasure to chronic disease and disability progression, and recent research has focused on its role in improvement of the inflammatory profile.

A large body of cross-sectional evidence reports that increased physical activity (PA) is associated with lower systemic inflammation.³ However, the same effect has not uniformly been seen in intervention studies. Data from several small-scale intervention studies suggest that exercise training diminishes inflammation.^{4–7} However, results from large (i.e. $n>20$ per treatment group), randomized, controlled (i.e. structured, center-based exercise interventions) trials (RCTs) designed to definitively test the effects of increased PA on inflammation are inconclusive.^{8–19} We previously showed that, in elderly men and women, 12 months of moderate-intensity PA lowers systemic concentrations of interleukin-6 (IL-6) and IL-8 relative to a non-PA health education intervention.^{15;19} However, several other measured inflammatory biomarkers (including CRP, IL-6sR, IL-1sRII, sTNFRI, sTNFRII, IL-15, adiponectin, IL-1ra, IL-2sR α , and TNF- α) were unchanged. Additional evidence from long-term, large RCTs is needed to elucidate the independent role of PA as a therapy for chronic inflammation.

One factor which may confound the relationship between exercise and inflammation is weight loss (WL), as WL can accompany exercise training and is correlated with improvement of the inflammatory profile.²⁰ In several observational cohort studies, adjustment for adiposity (most often measured by body mass index, or BMI), attenuates the strength of the relationship between inflammatory biomarkers and PA.^{21–23} Our previously described RCT did not induce WL,^{15;19} and may (at least in part) explain our modest findings. Therefore, the purpose of this study was to expand our previous research by determining the independent effect of long-term PA and the combined effects of long-term PA and WL on circulating levels of inflammatory biomarkers in overweight and obese, older community-dwelling adults at risk for CVD.

METHODS

Study Design

This study was conducted as an ancillary study to the Cooperative Lifestyle Intervention Program (CLIP), a RCT of PA and WL on mobility in overweight or obese older adults with, or at risk for, CVD. The study was conducted within the community infrastructure of North Carolina Cooperative Extension Centers in eight waves. 288 participants were

randomized to PA+WL, PA, or a successful aging (SA) education control arm. The primary study outcome was time (seconds) to complete a 400-m walk, with design details and main findings on physical function previously published.²⁴ The local institutional review board at Wake Forest University approved the study, and all study participants gave written informed consent to participate.

Study Participants

Eligibility criteria identified ambulatory, overweight or obese, community-dwelling older adults who either had CVD or cardiometabolic dysfunction and evidence of self-reported limitations in mobility. Detailed inclusion and exclusion criteria and a flow diagram of specific numbers of individuals screened and reasons for exclusion are published.²⁴ Briefly, the major inclusion criteria were age of 60–79 years, BMI >28 kg/m², self-reported mobility limitation, sedentary lifestyle, evidence of a recent CVD incident or metabolic syndrome diagnosis, and willingness to be randomized to any intervention group and sign an informed consent document. The major exclusion criteria were BMI >40 kg/m², inability to walk unassisted, inability to speak or read English, participation in another medical intervention study, or diagnosis of a condition that precluded participants from safely participating in the interventions (i.e. severe cardiac or metabolic disease, active cancer, or hearing/visual impairment).

Interventions

The PA intervention consisted of a combination of walking and interactive, group-mediated, behavioral focused sessions (48 total sessions) and was divided into two phases. For the first 6 months (intensive phase), 3 group sessions (90 minutes) and one individual session (30 minutes) per month were conducted in a supervised setting. Participants were asked to walk for 30 minutes on most days of the week (with a goal of 150 minutes of aerobic/walking exercise per week) at a moderate level of intensity (defined as a self-reported rating of perceived exertion of 13 on the Borg Scale). Accelerometers were used to monitor the intensity of PA achieved during exercise, with an average MET-level of 3 or greater recorded. During the next 12 months (maintenance phase), the frequency of contact was reduced (1 group session and 1 telephone contact per month). Discussion mirrored the check-in during the intensive phase (i.e. PA goals were discussed, specific plans of action were implemented, and self-regulatory skills were reinforced).

The combined intervention arm (PA+WL) involved the PA program (48 total sessions) in conjunction with dietary WL. The WL goal was to reduce caloric intake to produce a WL of approximately 0.3 kilograms per week for the first 6 months, for a total loss in mass of 7–10% of initial body weight. During the weight maintenance phase, participants were encouraged to continue WL as long as their BMI was >20 kg/m²; however, the primary focus was weight maintenance. Further details of both the PA and WL programs can be found in the primary outcome paper.²⁴

A SA health education intervention was used as the active control. Participants met in groups weekly for the first 8 weeks, monthly through the 6th month, and bimonthly until the end of the study (18 sessions total). Sessions included health topics relevant to older adults such as how the body changes with aging, prevention or delaying disease, eating for good health, positive attitudes toward aging, family relationships and care giving, and talking to health care providers.

Measurements

Participants were enrolled between January 2005 and April 2010. Baseline assessments included self-reported demographic, medical history, and co-morbidity information,

measured height and weight, physical activity energy expenditure, and time to walk 400 m.²⁵ Lifecorder-EX accelerometers (New-Lifestyles Inc, Lees Summit, Missouri) were used to assess physical activity in all participants. Participants were asked to wear the accelerometer for 7 days immediately after the baseline, 6- and 18-month assessment visits. Intensity levels 3 to 9 were classified as “moderate to vigorous”; consistent with the metabolic demands of activity for this age group. Follow-up visits occurred at 6-, 12- and 18-months and fasting blood samples were collected baseline, 6 and 18 months.

Inflammatory Biomarkers—All blood samples were collected from CLIP participants in the early morning after a 12-hour fast. The 6- and 18-month blood samples were collected at least 24 hours after the last acute bout of exercise. Blood sampling was postponed (1–2 weeks after recovery of all symptoms) in the event of an acute respiratory, urinary tract, or other infection. All blood was collected, processed, divided into aliquots, and stored in the Biological Specimen Repository at Wake Forest School of Medicine at –80°C until later analysis.

Ethylenediaminetetraacetic acid (EDTA) plasma samples were used to analyze all inflammatory biomarkers. Adiponectin, leptin, high sensitivity interleukin-6 (hsIL-6), IL-6 soluble receptor (IL6sR) and soluble tumor necrosis factor receptor 1 (sTNFR1) biomarker assays were completed by absorbance enzyme-linked immunosorbant assay (ELISA) methods using the R&D Systems (Minneapolis, MN) Quantikine kits. IL-8 was analyzed by chemiluminescent ELISA technique R&D Systems QuantiGlo kit. R&D Systems reports sensitivities (using the average minimum detection dose), the standard concentration ranges, and inter- and intra-assay coefficients of variation (CV) for each biomarker per lot number. These values are as follows: adiponectin (ng/ml): 0.25, 3.9–250, 6.5%, and 3.5%; leptin (pg/mL) <7.8, 15.6–1000, 4.4% and 3.2%; hsIL-6 (pg/mL): 0.04, 0.156–10, 7.8%, and 7.4%; IL-6sR (pg/mL): 6.5, 31.2–2000, 5.1% and 4.5%; sTNFR1 (pg/mL): 0.77, 7.8–500, 6.1%, and 4.4%; and IL-8 (pg/mL): 0.3, 1.6–5000, 8.2%, and 4.3%. All samples were measured in duplicate on the same plate, and the average of the two values was used for data analyses. Duplicate samples that did not provide a CV of less than 25% for adiponectin, leptin, hsIL-6, IL-6sR and sTNFR1, and 30% for IL-8 were reanalyzed. Values meeting the CV requirements were averaged for data analyses and reporting.

Statistical Analysis

Descriptive statistics were calculated by intervention group at baseline. Means and standard errors were calculated for each inflammatory biomarker, by intervention group and timepoint. Cytokines were log transformed for primary statistical analysis as raw data did not satisfy either the normality or linearity assumptions. Mixed model analysis of variance was used, as in the primary results paper,²⁴ with adjustment for baseline biomarker, wave, gender, and visit (6 or 18 months). Data were then back transformed as means and 95% confidence intervals by intervention group for ease of interpretation. To clarify the contribution of weight loss and physical activity intervention effectiveness, baseline and follow-up weight and PA level (based on accelerometry) were added as covariates to the primary analytic models, one model for weight loss and another for physical activity. To examine the impact of high/low baseline biomarker levels on treatment, we tested for interactions between the treatment allocation and a dichotomized biomarker (< median vs. median).

RESULTS

Baseline and Descriptive Characteristics

The average age of study participants was 67.0 ± 4.8 years, with the majority being white (82%) and female (67%). Most participants were classified as obese, with mean BMI by treatment group reported as: 33.1 ± 4.1 , 32.8 ± 3.9 , and 32.6 ± 3.5 , for the PA+WL, PA, and SA groups, respectively. Intervention adherence, as well as intervention effects on WL, is previously reported.²⁴ Briefly, attendance during the intensive and maintenance phases averaged $88.2 \pm 25.2\%$, $79.8 \pm 24.6\%$, and $70.9 \pm 26.5\%$ for the PA+WL, PA and SA groups, respectively. Participants in the WL+PA group lost 8.5% of initial body weight at 6 months (approximately 8 kg), and maintained losses through the 18-month follow-up, while follow-up weight in the PA and SA groups remained unchanged from baseline.

Effects of the Interventions on Inflammatory Biomarkers

Table 1 shows the means and standard errors for all inflammatory biomarkers in each intervention group over 18-months of follow-up, by timepoint. After adjustment for baseline biomarker, wave, gender, and visit, both leptin and hsIL-6 showed a significant intervention effect (Table 2). Specifically, leptin (ng/ml) was significantly lower in the PA+WL group compared to PA or SA [21.3 (95% CI: 19.7 – 22.9) vs. 29.3 (26.9 – 31.8) and 30.3 (27.9 – 32.8), respectively; both $p < 0.01$], and hsIL-6 (pg/mL) was also significantly lower in the PA+WL group compared to PA or SA [2.1 (95% CI: 1.9 – 2.3) vs. 2.5 (2.3 – 2.7) and 2.4 (2.2 – 2.6), respectively; both $p < 0.05$]. Interestingly, further adjustment for baseline and follow-up weight attenuated the previously significant intervention effect on hsIL-6 and leptin to non-significance ($p = 0.22$ and 0.75 , respectively); whereas adjustment for baseline and follow-up moderate physical activity level (assessed via accelerometry in all participants) had no bearing on intervention effectiveness ($p = 0.0151$ and < 0.0001 , respectively).

sTNFR1 (pg/mL) was marginally lower in the PA+WL group, compared to SA [1344 (1296 – 1393) vs. 1426 (1372 – 1482)], although results did not reach statistical significance (overall $p = 0.09$), and no intervention effect was observed for adiponectin, IL6sR or IL-8. Lastly, further analyses (using the same covariates as above in the main model) were performed to determine whether intervention effect was contingent on baseline biomarker level. There was no evidence of a differential treatment effect by high/low baseline biomarker levels (data not shown).

DISCUSSION

The purpose of this study was to determine the independent effect of long-term PA and the combined effects long-term PA and WL on circulating levels of inflammatory biomarkers in overweight and obese, older adults at risk for CVD. Results show that the combination of caloric restriction (resulting in WL) plus PA yielded greater reductions in leptin and hsIL-6 compared to PA alone or the SA intervention. Although not a consistent finding among all measured inflammatory biomarkers, results suggest that WL, more so than PA, is the lifestyle factor most responsible for improvements to the inflammatory profile in this population.

Although a large body of observational data shows that a higher volume of PA, independent of BMI, is associated with a lower systemic inflammation,³ there is limited data from RCTs adequately designed to study the effects of PA, independent of WL, on inflammation. To date, results from only two other RCTs have been published comparing the effects of exercise (and WL alone) to the combination of exercise and WL on inflammation. The most recent study randomized 79 obese men and women to 12-weeks of either: 1) exercise only, 2) diet-induced WL only, or 3) exercise and diet-induced WL combined.²⁶ Exercise only

decreased MCP-1, but did not alter IL-6, IL-18, IL-15, MIP-1 α or adiponectin, despite a 3.5% decrease in body weight. The diet groups, however, lost approximately 11% of their initial body weight, and showed decreases in MCP-1, IL-18, IL-15, MIP-1 α , and increases in adiponectin. In the combined group, IL-6 was also reduced. Interestingly, WL was a significant predictor of change in inflammatory status as the highest tertile of weight reduction (>14% of baseline weight lost) had a greater decrement in the inflammatory biomarkers (and an increase in adiponectin) compared to those achieving less WL (<3% of baseline weight lost), independent of group assignment.

A second study also investigated whether aerobic exercise training, with and without WL, had effects on several biomarkers of inflammation.¹⁰ This study utilized a 2x2 factorial design, where 360 obese older men and women with knee osteoarthritis were randomized to control, WL, exercise, or exercise plus WL for 18-months. Participants in the WL only and exercise plus WL groups lost 5.7% and 4.4% of their baseline body weight, respectively, while bodyweight did not significantly change in the exercise only group (-2.6%) relative to control (-1.3%). Compared to the non-WL groups, assignment to dietary WL resulted in greater reductions in circulating levels of CRP, IL-6 and sTNFR1; although, IL-6sR, TNF α , and sTNFR2 were unchanged. Overall, our findings are in agreement with published results, showing that the combination of PA and diet-induced WL is more effective in reducing overall chronic inflammation than PA alone.

Although causal mechanisms by which WL contributes to improvements in the inflammatory profile have not been fully elucidated, reduction in excess adipose tissue likely plays a role. It is well established that individuals with more adipose tissue have higher systemic levels of inflammatory biomarkers, including, among others, CRP, IL-6 and TNF α .^{27;28} Additionally, recent research has identified several adipose-derived and secreted cytokines, acute phase reactants, and metabolites.^{28;29} These “adipokines” can act in an autocrine, paracrine, or endocrine manner to affect metabolic functions of other tissues. While the secretion of inflammatory proteins by a single adipocyte or fat depot may be relatively small, excessive adiposity can have a large impact on the body’s physiologic homeostasis, including systemic inflammatory burden. Lastly, and in agreement with previously cited research, data examining the effect of surgical removal of fat mass on inflammation show a direct, significant relationship, with reduction in circulating inflammatory biomarkers following a targeted reduction in fat mass.³⁰ Collectively, these data suggest that obesity is characterized by a state of chronic inflammation, directly related to the amount of stored body fat, and reduction in body fat mass (via overall WL) is an effective means of reducing inflammatory burden.

Strengths of the current study design include measurement of multiple inflammatory biomarkers before and after the intervention period as well as inclusion of a weight-stable PA-only arm and a WL+PA arm to adequately assess the effect of PA on inflammation, independent of WL. However, the results of our study are limited to overweight and obese, older adults at risk for CVD as well as the select inflammatory biomarkers we chose to assess, and do not assess the effect of WL independent of PA. Although further analysis of the WL+PA group affirm other studies showing that changes in weight, rather than PA, is the more influential lifestyle factor, a study design including a WL-only group is needed to sufficiently test the hypothesis that WL alone, rather than the combination of WL+PA, can elicit favorable changes to the inflammatory profile in this population.

In conclusion, addition of dietary-induced WL to PA reduced circulating leptin and hsIL-6 compared to PA alone and to health education in overweight and obese, older adults at risk for CVD. Results implicate WL as the primary lifestyle factor responsible for reductions in

hsIL-6 and leptin. Future studies should address whether the combination of WL+PA is more effective than WL alone for improving inflammatory biomarkers in this population.

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Table 1

Raw inflammatory biomarker values at each timepoint, according to intervention group.

Inflammatory Biomarker	PA + WL (n=98)			PA (n=97)			SA (n=93)		
	Baseline	6-months	18-months	Baseline	6-months	18-months	Baseline	6-months	18-months
Adiponectin (ng/mL)	7298±621	7590±617	7860±614	6923±409	6892±454	6731±416	9023±743	8316±608	8800±660
Leptin (ng/mL)	44.0±3.1	29.6±3.0	36.1±3.8	38.0±2.6	34.9±2.7	37.3±2.7	37.9±2.3	36.8±2.6	40.6±3.0
hsIL-6 (pg/mL)	2.9±0.2	2.8±0.2	2.5±0.2	2.8±0.2	3.1±0.2	2.9±0.2	2.6±0.2	2.9±0.2	2.7±0.2
IL-6sR (pg/mL)	40408±1308	40423±1248	38791±1267	40556±1367	40821±1513	39963±1431	40973±1141	40495±1304	40505±1325
IL-8 (pg/mL)	3.3±0.2	3.3±0.4	2.8±0.2	3.6±0.3	3.6±0.3	3.1±0.2	4.8±1.2	4.1±0.6	3.8±0.5
sTNFR1 (pg/mL)	1611±57	1562±54	1521±55	1544±64	1578±74	1552±76	1507±56	1496±54	1488±56

Data are presented as means and standard errors (SE). Values are adjusted for baseline biomarker, wave, gender, and visit. PA = physical activity; WL = weight loss; SA = successful aging; hsIL-6 = high sensitivity interleukin-6; IL6sR = interleukin-6 soluble receptor; IL-8 = interleukin-8; sTNFR1 = soluble tumor necrosis factor 1; ng = nanogram; pg = picogram; mL = milliliter.

Table 2

Post-intervention means of inflammatory biomarkers.

Biomarker	PA+WL			PA			SA			Overall <i>p</i> -value
	Mean	95% CI		Mean	95% CI		Mean	95% CI		
Adiponectin (ng/mL)	6532	(6101–6993)		5898	(5477–6351)		6351	(5907–6827)		0.13
Leptin (ng/mL)	21.3	(19.7–22.9)		29.3	(26.9–31.8)		30.3	(27.9–32.8)		<0.0001
hsIL-6 (pg/mL)	2.1	(1.9–2.3)		2.5	(2.3–2.7)		2.4	(2.2–2.6)		0.02
IL6sR (pg/mL)	37866	(36373–39422)		38189	(36545–39906)		38948	(37316–40651)		0.63
IL-8 (pg/mL)	2.5	(2.3–2.7)		2.8	(2.5–3.0)		2.8	(2.6–3.1)		0.12
sTNFR1 (pg/mL)	1344	(1296–1393)		1384	(1331–1440)		1426	(1372–1482)		0.09

Data were analyzed on the log-adjusted scale, but results are presented as means and 95% confidence intervals after transforming back to the original scale. Analyses were adjusted for the log baseline biomarker, wave, gender, and visit. PA = physical activity; WL = weight loss; SA = successful aging; hsIL-6 = high sensitivity interleukin-6; IL6sR = interleukin-6 soluble receptor; IL-8 = interleukin-8; sTNFR1 = soluble tumor necrosis factor 1; ng = nanogram; pg = picogram; mL = milliliter.