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# Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study

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**Christiansen T, Paulsen SK, Bruun JM, Pedersen SB, Richelsen B.** Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. *Am J Physiol Endocrinol Metab* 298: E824–E831, 2010. First published January 13, 2010; doi:10.1152/ajpendo.00574.2009.—The purpose of this study was to investigate the effect of exercise training and diet-induced weight loss alone or in combination on inflammatory markers in circulation, in adipose tissue (AT) and in skeletal muscle (SM) in obese subjects. Seventy-nine obese subjects were randomized into a 12-wk intervention: *1*) exercise only (EXO), *2*) diet-induced weight loss using a very low energy diet (DIO), and *3*) exercise and diet-induced weight-loss combined (DEX). Blood samples (metabolic and inflammatory markers) and AT and SM biopsies (mRNA expression) were collected at baseline and after 12 wk. In the EXO group the weight loss was 3.5 kg and in the DIO and DEX groups it was 12 kg in both. $\dot{V}O_{2max}$ was increased by 14–18% in the EXO and DEX groups with no changes in the DIO group. In the DIO and DEX groups, circulating levels of MCP-1, MIP-1α, IL-15, and IL-18 were decreased, and adiponectin was increased ($P < 0.05$ for all). In the EXO group, MCP-1 was decreased with 10% ($P = 0.06$). By combining the weight loss in all three groups, we found a correlation between the degree of weight loss and improvement in several of the inflammatory markers ($P < 0.05$). In AT biopsies, subjects in the DIO and DEX groups achieved a general beneficial but nonsignificant effect on the gene expression of inflammatory markers. In the EXO group, no changes in AT adipokine mRNA were found except for an increment of adiponectin ($P < 0.05$). In SM, the only observed change was that the gene expression of IL-6 was increased in all three groups ($P < 0.05$). In conclusion, rather large weight losses (>5–7%) were found to have beneficial effects on circulating inflammatory markers in these obese subjects. Aerobic exercise for 12 wk, which increased $\dot{V}O_{2max}$, was found to have no effects on circulating inflammatory markers in these obese patients. It is suggested that more intensive exercise may be necessary to affect systemic inflammation.

inflammation; exercise; weight loss; adipose tissue; skeletal muscle

WEIGHT LOSS AND PHYSICAL ACTIVITY ALONE and in combination can improve several of the components in the metabolic syndrome and have been shown to have beneficial effects in the prevention of type 2 diabetes (29, 31, 35, 48), but the mechanisms involved in these positive effects are not fully understood. Chronic low-grade inflammation is associated with obesity and a sedentary lifestyle (2, 15). Low-grade inflammation is an independent risk factor for development of type 2 diabetes and cardiovascular disease and is closely associated with the metabolic syndrome. With increasing adiposity, adipose tissue (AT) is found to secrete a variety of inflammatory proteins (adipokines) with autocrine and paracrine effects as well as with systemic effects (16). These adipokines are suggested to mediate some of the health complications associated with obesity either through a hormonal effect on other organs such as the liver, muscle, or endothelial cells or through a local effect in AT (local inflammation and local insulin resistance) (50). Expansion of AT as seen in obesity leads to recruitment of macrophages into AT (52). Macrophages in AT play a central role in the production of adipokines (19). The initial stimulation to recruit macrophages to AT is not fully elucidated, but chemokines such as macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1), synthesized by the AT, might play a central role in this recruitment.

Among the proinflammatory cytokines, interleukin-15 (IL-15) is a newer factor that may be related to obesity and obesity-related complications such as cardiovascular diseases. IL-15 is suggested to act as an antiadipogenic cytokine, since cell culture studies have shown that IL-15 inhibits preadipocyte differentiation, and administration of IL-15 to rodents is shown to be associated with a decrease in fat mass (9). In humans, circulating levels of IL-15 have been found inversely associated with trunk fat mass (39), and very recently IL-15 has been found decreased in obese subjects compared with lean controls (4). Thus, IL-15 may be involved in regulating fat mass/fat distribution. IL-15 is expressed in macrophages, endothelial cells, fibroblasts, and muscle cells among other cell types (10). Moreover, IL-15 has been associated with the degree of coronary artery disease and has been involved in the development of atherosclerosis (25), where IL-15 may contribute to the destabilization of the plaques by its activation of T cells, which induce production of mediators with plaque-destabilizing properties, such as TNF-α and matrix metalloproteinase-9 (46). MIP-1α has also been recently linked to the obese state, as the gene expression of MIP-1α has been found increased in visceral and subcutaneous abdominal fat of obese subjects compared with lean subjects (26). Moreover, MIP-1α is found present in atherosclerotic lesions, where it is suggested to participate in the early progression of the atherosclerotic process (53). Recently, circulating levels of MIP-1α were shown elevated during acute coronary syndrome and found to be a strong predictor of future cardiovascular events (17).The effect of weight loss and exercise on IL-15 and MIP-1α has still not been fully elucidated.

We (13) and others (33) have documented that weight loss (diet and surgically induced) is able to improve the metabolic syndrome and the inflammatory state in obese subjects. The

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weight loss-induced reduction in inflammatory markers in the circulation is often associated with a normalization of the production and the gene expression of inflammatory markers in the AT (8, 14). It is still unknown, however, whether the weight loss-induced reduction of inflammation in AT is causally related to the systemic improvement in inflammation associated with weight loss.

Since exercise training is generally inversely associated with the level of inflammatory markers in the circulation, it is suggested that chronic muscle work may induce a general anti-inflammatory effect (42). Skeletal muscle (SM) expresses IL-6, IL-8, and IL-15 (41) and as the increase in plasma IL-6 during strenuous exercise is followed by increased levels of the anti-inflammatory protein IL-10, it is suggested that the muscle-derived IL-6 could be involved in mediating an anti-inflammatory environment (42). However, so far the effect of exercise on obesity-related chronic inflammation has provided conflicting results (27, 30, 34, 38, 40, 43).

Moreover, since exercise training is generally associated with a modest but significant reduction in fat mass (FM) (11), it is not known whether the effect of exercise on the inflammatory profile is due to the reduction of FM or due to the exercise-induced muscle work per se.

Thus, when the effect of exercise on the systemic inflammation is investigated, the exercise-induced changes in body weight must be taken into consideration. A study combining exercise training with diet restriction, and keeping the weight loss equivalent to the weight loss induced with diet restriction alone, could therefore be a method to investigate the independent effect of exercise on the inflammatory profile.

The aim of the present study was to investigate the independent and the combined effects of exercise and weight loss on metabolic factors and inflammation in obese subjects to determine whether exercise training per se, independent of exercise-induced weight loss, has anti-inflammatory effects. The study was a 12-wk randomized intervention with three groups of obese subjects: *1*) exercise alone (EXO), *2*) hypocaloric diet only (DIO), and *3*) hypocaloric diet only plus exercise only (DEX), where the weight loss was kept similar to that of *group 2*. The inflammatory markers were determined both in the blood circulation (proteins) and in fat and muscle biopsies (gene expression). In addition, the metabolic profiles of these obese subjects was determined.

## MATERIALS AND METHODS

### *Subjects*

Seventy-nine obese but otherwise healthy males and females were recruited via advertisements in local newspapers. The subjects were eligible for inclusion if they were aged 18–45 yr, obese (BMI 30–40 kg/m$^2$), physically inactive (<30 min/day) and weight stable for at least 3 mo (±2 kg of current body wt). Exclusion criteria were cardiovascular disease, type 2 diabetes, pregnancy, or orthopedic difficulties causing inability to undertake an exercise program. No subjects received medication that could affect the investigated metabolic markers. Prior to participation, the subjects gave a written informed consent. The study was approved by the local ethics committee in the county of Aarhus and followed the principles outlined in the Declaration of Helsinki. The 79 obese subjects were randomized into the 12-wk intervention study consisting of *1*) exercise only (EXO, $n = 25$, 12 females, 13 males), *2*) hypocaloric diet only (DIO, $n = 29$, 14 females, 15 males), or *3*) hypocaloric diet only and exercise only (DEX, $n = 25$, 12 females, 13 males). As previously reported, 20 subjects did not complete the study (8 women and 12 men; BMI 35.7 ± 4 kg/m$^2$; $P = 0.2$ vs. subjects who completed the study) (12). According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP3) definitions of the metabolic syndrome (1), 50% (13 females and 16 males) of all the obese subjects who completed the study had at baseline the metabolic syndrome.

We performed a sample size calculation using MCP-1 as our primary end point and found that, to show a minimal relevant difference of 40 pg/ml between the weight loss groups and the exercise group, 20 subjects were needed in each group.

### *Study Design*

*Diet regimen.* Subjects in the DIO and DEX groups were prescribed a liquid very low energy diet (VLED; Nupo, Copenhagen, Denmark) of, respectively, 600 and 800 kcal/day (proteins 41 g, carbohydrates 29 g, fat 5.6 g per 100 g) for 8 wk followed by a weight maintenance diet for 4 wk. In these two groups, we intended for the subjects to obtain similar weight losses to observe the possible specific, weight-independent, effect of exercise. Thus, the subjects in the DEX group were allowed to consume 150–200 kcal more per day than the DIO group, reflecting the estimated extra energy expenditure of 1,500 kcal/wk during exercise activity. The dietary intake in the EXO group through the intervention and the energy content during the weight maintenance phase in the DIO and DEX groups have previously been described (12). Briefly, the daily energy requirement for the subjects during the weight maintenance period was determined by estimating resting energy expenditure multiplied by a factor of 1.5 for subjects in the DIO group and 2.5 in the DEX group. The energy contents during this period consisted of 55% from carbohydrates, 15% from protein and less than 30% from fat.

*Exercise regimen.* The exercise intervention for subjects in the EXO and the DEX groups consisted of supervised aerobic exercise three times per week with duration of 60–75 min per training session, with an estimated energy expenditure of 500–600 kcal per session. The subjects were required to keep records of training sessions during the whole intervention.

### *Maximal Rate of Oxygen Uptake*

At baseline and after 12 wk, each subject completed a progressive maximal exercise test using a stationary cycle ergometer (Monark 828; Monark Exercise, Vansbro, Sweden) and standard open-circuit spirometry techniques (AMIS 2001; Innovision, Odense, Denmark).

### *Anthropometry and Metabolic Risk Factors*

At baseline and after 12 wk anthropometrics and blood pressure were measured as previously described (12). Blood samples were collected after an overnight fast and at least 24 h after the subjects had finished the last exercise session.

*AT and SM biopsies.* At baseline and after *week 12*, the AT biopsies were obtained from the abdominal subcutaneous AT depot 5–10 cm lateral to the umbilicus. Briefly, the skin was anesthetized with lidocaine (10 mg/ml) before a small incision was made, and ≈200 mg of AT was removed under sterile conditions using a liposuction needle. Immediately after removal, the AT sample was washed in isotonic NaCl, snap-frozen in liquid nitrogen, and kept at −80°C until RNA extraction. The SM biopsies taken were obtained from the vastus lateralis muscle. Skin and muscle fascia were anaesthetized with lidocaine (10 mg/ml), and under sterile conditions a 1-cm incision was made, whereafter ≈100 mg of muscle tissue was removed using the conchotome biopsy technique. The SM biopsies were dissected free of visible fat, snap-frozen in liquid nitrogen, and kept at −80°C until mRNA extraction. To minimize a carryover effect of the last exercise bout, the biopsies in AT and SM were taken 24–48 h after the last exercise bout.

*Determination of inflammatory markers, plasma lipids, glucose, and insulin.* IL-6 was measured with a highly sensitive ELISA assay (R&D systems, Minneapolis, MN). IL-15, MCP-1, and MIP-1α were measured with a human ELISA DuoSet (R&D Systems), IL-18 was measured with a human ELISA KIT (MBL Japan). Adiponectin was measured using a human-specific highly sensitive ELISA method (b-Bridge International). Cholesterol, triglycerides, and glucose were analyzed at the local University Department of Clinical Biochemistry. Insulin was analyzed with an enzyme-linked immunosorbent assay (DAKO, Cambrigdeshire, UK). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated using the formula: fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 (37).

*mRNA isolation and RT-PCR analysis.* RNA was isolated as previously described (7). The mRNA levels of the target genes in AT were expressed relative to the housekeeping gene $\beta_2$-microglobulin, whereas the mRNA levels of the target genes in SM were expressed relative to the housekeeping gene β-actin. Quantification was performed with a SYBR Green real-time PCR assay using an iCycler PCR machine (Bio-Rad Laboratories, Hercules, CA). All samples were determined in duplicate. The threshold cycle ($C_T$) was calculated and the relative gene expression of housekeeping gene to target gene was calculated as $1/2^{(C_{T\ target} \div C_{T\ \beta 2\text{-microglobulin}})}$, essentially as described in the *User Bulletin no. 2*, 1997 from PerkinElmer (PerkinElmer Cetus, Norwalk, CT).

The sequences of the oligonucleotide primer pairs were tested on the human genome by use of the BLAST modality in the NCBI database (http://blast.ncbi.nlm.nih.gov/Blast.cgi) and afterward tested on random samples of various human tissues by our laboratory. The primer pairs are listed in Table 1. Before analysis of any target genes, the housekeeping genes were tested for stability during the intervention in random samples from the three intervention groups. In AT samples and SM samples, $\beta_2$-microglobulin and β-actin, respectively, were stable during the intervention in all three groups, displaying comparable number of $C_T$ cycles, and therefore were suitable as housekeeping genes.

### *Statistical Analysis*

Descriptive statistics for anthropometrics and metabolic risk markers are presented as means ± SD. McNemar's test was used to test changes in nominal data during the intervention. A two-way ANOVA (treatment and sex) with repeated measurements was performed to analyze the effect of treatment on anthropometrics and inflammatory markers. A one-way ANOVA was performed to analyze the impact of weight loss on the inflammatory markers. Post hoc analysis was performed with Bonferroni adjustment. The chosen significance level was a two-tailed $P$ value of $<0.05$. The statistical software packet SPSS (SPSS, Chicago, IL) was used for all calculations.

## RESULTS

### *Changes in Weight, Metabolic Risk Factors, and Inflammatory Markers*

Subjects in the EXO group obtained a weight loss of 3.5% (3.5 ± 3 kg, $P < 0.01$) after 12 wk. Changes in body weight during the VLED period in the DIO group were 10.5% (11.2 kg) and in the DEX group 11.1% (12.1 kg), respectively (data not shown). These weight losses were maintained during the subsequent 4 wk of the weight maintenance period (Table 2). Subjects in the EXO and DEX groups increased their $\dot{V}O_{2max}$ with 18 and 14%, respectively ($P < 0.01$ vs. baseline), whereas there was no change in the DIO group (Table 2). Values of the metabolic parameters (baseline and *week 12*) are shown in Table 2. After the intervention, a significant decrease in the number of subjects with the metabolic syndrome was observed in both the DIO group and the DEX group (both $P < 0.05$; Table 2). In all three groups, similar significant reductions in blood pressure and total cholesterol were found (Fig. 1). Triglycerides were reduced similarly in the DIO and DEX groups, and these reductions were significantly higher compared with the changes in the EXO group ($P < 0.01$; Fig. 1). Only in the DEX group was a significant increase in HDL-cholesterol observed ($P < 0.01$; Fig. 1). In the DIO and DEX groups, glucose, insulin, and HOMA-IR were reduced with 7–26% (all $P < 0.01$ vs. baseline; Fig. 1). In the EXO group, HOMA-IR was nonsignificantly reduced ($P = 0.09$) and FFA was reduced significantly by 17% ($P < 0.05$) (Fig. 1).

The absolute values of the circulating level of inflammatory markers at baseline and after 12 wk are presented in Table 3. In the EXO group, circulating MCP-1 was reduced by 10%; ($P = 0.06$) after the 12-wk intervention. MIP-1α, IL-6, IL-8, and IL-15 were not affected by exercise training (Fig. 2). In the hypocaloric diet-induced weight loss groups with and without exercise (DEX and DIO), a general and comparable decrease in most inflammatory markers was observed. MCP-1 was reduced by ≈16% in both groups ($P < 0.01$), IL-15 by 24–26% ($P < 0.01$), MIP-1α by 14% ($P < 0.05$), and IL-18 by 16% ($P < 0.01$; Fig. 2). IL-6 was significantly reduced only in the DEX group ($P < 0.05$; Fig. 2). Adiponectin was significantly increased in the DIO and DEX groups ($P < 0.01$; Fig. 2) but no changes were observed in the EXO group.

Table 1. *Oligonucleotide primer pairs used for mRNA determination*

| | Sense Primer | Antisense Primer |
|---|---|---|
| IL-6 | 5′-AAATGCCAGCCTGCTGACGAAG-3′ | 5′-AACAACAATCTGAGGTGCCCATGCTAC-3′ |
| II-10 | 5′ TCAAGGCGCATGTGAACTC 3′ | 5′ AGGGAAGAAATCGATGAC-3′ |
| II-15 | 5′ GTCTTCATTTTGGGCTGTTTCAGT 3′ | 5′ CCTCACATTCTTTGCATCCAGATTCT 3′ |
| TNF-α | 5′-CGAGTGACAAGCCTGTAGC-3′ | 5′-GGTGTGGGTGAGGAGCACAT-3′ |
| Adiponectin | 5′-CATGACCAGGAAACCACGACT-3′ | 5′-TGAATGCTGAGCGGTAT-3′ |
| Leptin | 5′ GATGACACCAAAACCCTCATC 3′ | 5′ GCCACCACCTCTCTGGAGTAG 3′ |
| MCP-1 | 5′-CGACATCCTGGAACTGCCCTACC-3′ | 5′-CACTGTGCCGCTCTCGTTCAC-3′ |
| MIP-1α | 5′ TCTTGGCTCTGCTGACACTCG 3′ | 5′ CACTGGCTGCTCGTCTCAAAG 3′ |
| CD-14 | 5′-TAAAGGACTGCCAGCCAAGC-3′ | 5′-AGCCAAGGCAGTTTGAGTCC-3′ |
| CD-68 | 5′-GCTACATGGCGGTGGAGTACAA-3′ | 5′-ATGATGAGAGGCAGCAAGATGG-3′ |
| $\beta_2$-MicroG | 5′ TCTCTCTTTCTGGCCTGGAG 3′ | 5′ AATGTCGGATGGATGAAACC 3′ |
| β-Actin | 5′-ACGGGGTCACCCACACTGTGC-3′ | 5′-CTAGAAGCATTTGCGGTGGACGATG-3′ |

MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; $\beta_2$-MicroG, $\beta_2$-microglobulin.

Table 2. *Baseline values and values at week 12*

| | EXO | | DIO | | DEX | |
|---|---|---|---|---|---|---|
| | Baseline | *Week 12* | Baseline | *Week 12* | Baseline | *Week 12* |
| *N* (F, M) | 19(10♀, 9♂) | | 19(9♀, 10♂) | | 21(11♀, 10♂) | |
| Age, yr | 37.2 ± 7 | | 35.6 ± 7 | | 37.5 ± 8 | |
| Weight, kg | 100.7 ± 10 | 97.2 ± 9 | 107.8 ± 12 | 95.5 ± 11 | 105.8 ± 15 | 93.5 ± 13 |
| BMI, kg/m$^2$ | 33.3 ± 4 | 32.2 ± 4 | 35.3 ± 4 | 31.2 ± 4 | 34.2 ± 3 | 30.3 ± 3 |
| Waist, cm | 104.1 ± 6 | 98.8 ± 5 | 110.8 ± 9 | 99.4 ± 9 | 109.5 ± 10 | 97.3 ± 9 |
| Systolic BP, mmHg | 126 ± 15 | 118 ± 8 | 129 ± 10 | 122 ± 12 | 140 ± 17 | 129 ± 18 |
| Diastolic BP, mmHg | 76 ± 12 | 68 ± 9 | 78 ± 12 | 82 ± 12 | 82 ± 12 | 72 ± 13 |
| Total cCholesterol, mmol | 5.5 ± 1 | 5.1 ± 0.8 | 5.0 ± 0.7 | 4.6 ± 0.9 | 5.6 ± 0.8 | 5.0 ± 0.9 |
| HDL-cholesterol, mmol/l | 1.3 ± 0.4 | 1.3 ± 0.5 | 1.2 ± 0.3 | 1.2 ± 0.3 | 1.2 ± 0.3 | 1.3 ± 0.3 |
| Triglyceride, mmol | 1.6 ± 0.7 | 1.5 ± 0.4 | 1.5 ± 0.5 | 1.1 ± 0.3 | 1.8 ± 0.6 | 1.2 ± 0.5 |
| Glucose, mmol | 5.6 ± 0.4 | 5.6 ± 5 | 5.5 ± 0.6 | 5.1 ± 0.5 | 5.6 ± 0.4 | 5.4 ± 0.5 |
| Insulin, pg/l | 65.0 ± 30 | 52 ± 26 | 86 ± 39 | 63 ± 38 | 89 ± 40 | 56 ± 28 |
| Free fatty acids, mmol | 0.6 ± 0.2 | 0.5 ± 0.2 | 0.5 ± 0.2 | 0.5 ± 0.2 | 0.6 ± 0.2 | 0.6 ± 0.3 |
| HOMA | 2.3 ± 1 | 1.8 ± 1 | 3.1 ± 2 | 2.1 ± 1 | 3.2 ± 2 | 2.0 ± 1 |
| Metabolic syndrome[1] (no/yes) | 12/7 | 16/3 | 8/11 | 18/1* | 7/14 | 18/3* |
| $\dot{V}O_{2max}$, l/min | 2.8 ± 0.7 | 3.3 ± 0.8 | 2.8 ± 0.7 | 2.8 ± 0.8 | 3.0 ± 0.6 | 3.4 ± 0.8 |

Baseline and *week 12* data are presented as means ± SD. EXO, exercise only; DIO, diet-induced only (very low energy diet); DEX, diet and exercise combined. [1]NCEP ATP3 definitions. *$P < 0.05$ vs. baseline

### *Impact of Weight Loss on Circulating Inflammatory Markers*

To investigate the association between the degree of weight loss and changes in circulating inflammatory markers, we divided all subjects in the three groups into tertiles in relation to their achieved weight loss. We found that subjects in the highest tertile of weight loss (mean weight reduction −14.5%, range −11.7 to −20.3%) compared with subjects in the lowest tertile (mean weight loss −3%, range 2.6% to −5.7%) had a higher decrement in MIP-1α ($P < 0.05$) and IL-15 ($P < 0.05$) and a higher increment in adiponectin ($P < 0.01$) (Fig. 3). Across the three groups, the changes in body weight were inversely associated with changes in adiponectin ($r = -0.45$, $P < 0.01$) and associated with changes in MIP-1α ($r = 0.3$, $P < 0.05$) and IL-15 ($r = 0.35$, $P < 0.05$), independent of changes in $\dot{V}O_{2max}$ (data not shown).

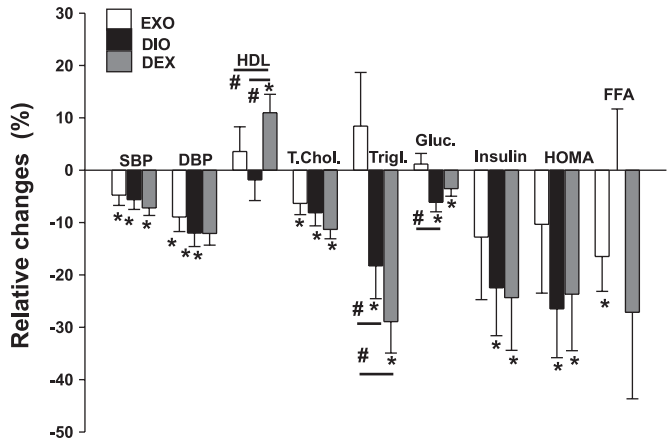


Fig. 1. Changes in metabolic risk factors: changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), HDL-cholesterol (HDL), total cholesterol (T.Chol), triglyceride (Trigl.), glucose (Gluc.), insulin, homeostasis model assessment (HOMA), and free fatty acids (FFA). Exercise only (EXO), hypocaloric diet only (DIO), and exercise only plus hypocaloric diet only combined (DEX). Data are shown as percentage changes in relation to baseline values. *$P < 0.01$ vs. baseline, #$P < 0.01$ vs. changes in EXO.

Of importance, no sex differences were observed within the three groups regarding relative changes or absolute changes in any of the inflammatory markers (data not shown).

### *Gene Expression of Inflammatory Markers in AT and SM*

In AT, no significant changes in adipokine gene expression besides an increase in adiponectin ($P < 0.01$) were observed in the EXO group (Fig. 4). In the DIO and DEX groups, leptin mRNA was, as expected, reduced ($P < 0.01$ vs. baseline and EXO group) and adiponectin mRNA was increased in both groups ($P < 0.01$) (Fig. 4). In the two weight loss groups (DIO and DEX), IL-6 was nonsignificantly decreased by 9–50%, TNF-α by 10–26%, MIP-1α by 24–36%, and MCP-1 by 7–27% (all with $P = 0.1$–$0.2$ vs. baseline). The macrophage-specific markers CD-68 and CD-14 were also investigated in AT. In the DIO group, CD14 was significantly reduced by 24% ($P < 0.01$ vs. baseline; Fig. 4). The changes in CD-68 were not significant in any of the groups compared with baseline.

The changes in gene expression of inflammatory markers in SM in the three groups were generally small, and there were no significant changes among the three groups after the interventions (Fig. 5). In relation to baseline levels, a general increment of the measured inflammatory markers was observed in all three groups. IL-6 was increased by 34–50% ($P < 0.05$), and IL-15 was increased by up to 20% ($P > 0.05$). The macrophage marker CD-68 was increased significantly in SM in the two diet groups (DEX and DIO) by ~40% ($P < 0.05$). The anti-inflammatory marker IL-10 was increased by 40–80% ($P > 0.05$).

## DISCUSSION

The obese state is characterized by low-grade inflammation, which is suggested to be of importance for the metabolic syndrome, for type 2 diabetes, and for cardiovascular diseases (15). In the present study, we found a general decrement in the proinflammatory markers in the circulation in response to marked weight loss (11%) in the two diet restriction groups. This may be of clinical interest and add to previous findings

Table 3. *Baseline values and values at week 12 in inflammatory markers*

| | EXO | | DIO | | DEX | |
|---|---|---|---|---|---|---|
| | Baseline | *Week 12* | Baseline | *Week 12* | Baseline | *Week 12* |
| IL-6 | 3.2 ± 2.4 | 2.5 ± 1.6 | 2.6 ± 1.6 | 2.4 ± 1.0 | 2.9 ± 1.6 | 1.9 ± 0.9 |
| IL-18 | 115.6 ± 34 | 107.6 ± 34 | 134.9 ± 48 | 110.3 ± 35 | 106.7 ± 34 | 89.2 ± 25 |
| IL-15 | 97.7 ± 152 | 101 ± 147 | 177.7 ± 193 | 106.4 ± 116 | 116.4 ± 191 | 78 ± 105 |
| MIP-1α | 283 ± 292 | 294 ± 296 | 331 ± 306 | 298 ± 302 | 233 ± 216 | 213 ± 222 |
| MCP-1 | 244.1 ± 86 | 218.2 ± 89 | 264.7 ± 207 | 224.8 ± 180 | 255 ± 216 | 216.3 ± 98 |
| Adiponectin | 9.2 ± 3.2 | 8.7 ± 3.4 | 7.4 ± 2.9 | 8.9 ± 4.1 | 7.8 ± 2.3 | 9.2 ± 3.0 |

Baseline and *week 12* data are presented as means ±SD.

where we and others have shown that weight loss in obese subjects is beneficial in improving the low-grade inflammatory state associated with obesity (7, 8, 13, 36), but we found no additional effect of exercise on the inflammatory profile. Of the newer inflammatory markers related to obesity, we found that MIP-1α and IL-15 were significantly reduced in the DIO and DEX groups, with no effects in the EXO group. IL-15 has been found to be highly expressed in muscle tissue, and it is suggested to have regulatory effects on the amount of body fat, maybe particularly through a reduction of the trunk fat mass that has been found at least in mice overexpressing IL-15 in skeletal muscle (44). In the present study, however, we found no associations between IL-15 and any measures of fat distribution. Since chemokines such as IL-15 and MIP-1α are considered to contribute significantly to the atherosclerotic process through accumulation and activation of leukocytes in the vascular wall promoting a vascular inflammation, the weight loss-induced reduction of both IL-15 and MIP-1α may have generally beneficial effects. A potential bias in investigating the independent effect of exercise on inflammatory markers in circulation could be the inability to dissociate between the effects of exercise itself from the confounding effect of the exercise-induced loss of fat mass (6, 32). In a group of sedentary obese males, it was found that 12 wk of exercise training without weight loss but with a decrease in waist circumference was associated with improvements in the metabolic risk profile and a decrease in the proinflammatory marker IL-6 (18). Thus, exercise may, besides its known beneficial effect on the metabolic profile, also exert an anti-inflammatory effect independently of weight loss. However, this was not found in the present study, where, in order to observe the possible specific, weight independent, effect of exercise we intended for the subjects in the two weight loss groups (DIO and DEX) to obtain similar weight losses. We found that subjects in the DIO and DEX groups, besides the similar weight losses (DIO group 11% and DEX group 11%) and comparable improvements in the metabolic profile, achieved similar decrements in proinflammatory markers (IL-6, IL-15, IL-18, MCP-1, and MIP-1α) and increment in the anti-inflammatory adipokine adiponectin. The lack of an independent effect of exercise on the circulating inflammatory profile could be due to the massive impact of the weight loss obtained by the diet (~,12 kg) and it is therefore unknown whether exercise would have had additional effects combined with more moderate weight losses. Exercise studies inducing large weight losses (49) or exercise studies including subjects with metabolic disorder, such as subjects with impaired glucose tolerance(40, 47), type 2 diabetes (27), or chronic heart failure (3, 22) have shown a decrease in proinflammatory markers in the circulation such as IL-6, MCP-1, high-sensitivity C-reative protein, IL-18, and TNF-α and an increase in anti-inflammatory makers such as adiponectin and IL-10. In

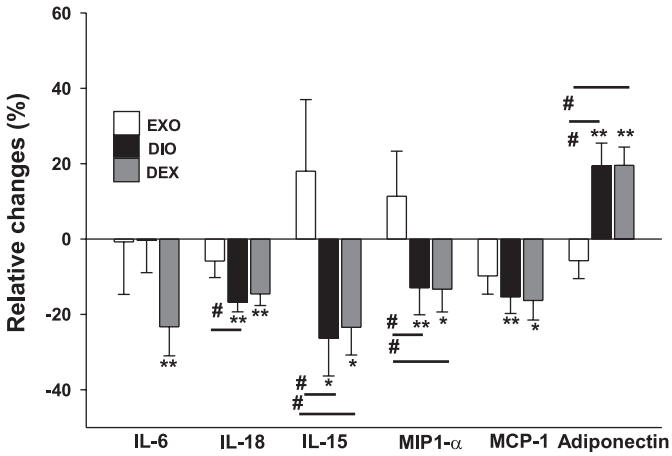


Fig. 2. Changes in circulating inflammatory cytokines. Relative changes in serum levels of IL-6, IL-18, IL-15, macrophage inflammatory protein-1α (MIP-1α), monocyte chemoattractant protein-1 (MCP-1), and adiponectin after 12 wk in EXO, DIO, and DEX. Data are shown as percentage changes in relation to baseline values. *$P < 0.05$ vs. baseline, ** $P < 0.01$ vs. baseline, #$P < 0.05$ vs. changes in EXO.

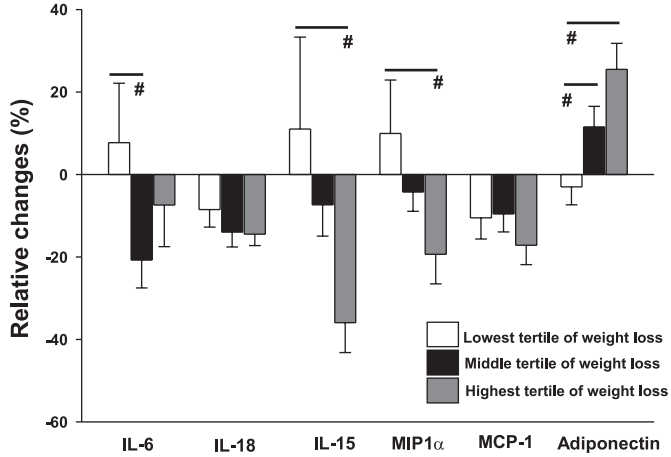


Fig. 3. Changes in circulating inflammatory cytokines in relation to degree of weight loss. Relative changes in serum levels of IL-6, IL-15, IL-18, MCP-1, MIP-1α, and adiponectin after 12 wk in relation to degree of weight loss. In the lowest tertile, mean weight loss was 3%, in the middle tertile, mean weight loss was 9%, and in thehighest tertile, mean weight loss was14.5%. #$P < 0.05$ vs. changes in lowest tertile group.

relation to the metabolic profile we found an effect of exercise training on traditional metabolic risk markers with significant reductions in blood pressure, total cholesterol, and FFA and a trend toward an increase in insulin sensitivity. As an increased circulating level of FFA has been shown to be associated with impaired insulin action in the liver and muscle, leading to insulin resistance, the observed decrease in circulating FFA may be of clinical importance. Degree of weight loss has previously been shown to be of importance for the improvement in circulating inflammatory markers (20), and in accord with this we found that subjects achieving weight losses above 14% (highest tertile of weight reduction) had a more pronounced decrement in circulating proinflammatory adipokines (and an increase in adiponectin) than subjects achieving a minor weight loss (<3%). It has previously been shown that marked calorie restriction is accompanied by regulation of a wide variety of inflammation-related molecules in human AT (14). As non-fat cells, and in particular macrophages, accumulating in AT has been shown to be responsible for most of the production of adipokines, with the exception of leptin and adiponectin, a reduction of AT-accumulated macrophages might mediate a decrease in low-grade inflammation. This is supported by the observation that a decrease in the two macrophage-specific markers CD-14 and CD-68 in response to weight loss has been shown to be associated with a decrease in the AT expression of proinflammatory markers and an increase in anti-inflammatory markers (7). In the present study, however, besides a decrease in CD-14 in the DIO group, we did not observe an effect on these macrophage-specific markers. Moreover, we found that only the two AT-specific proteins leptin and adiponectin were significantly affected by the weight loss.

It was recently shown that muscle macrophage number is increased with obesity and insulin resistance (51), and it was suggested that elevated levels of FFA synergizing with macrophages in SM exacerbate the inflammatory state of muscle cells, resulting in impaired insulin signaling (5). Thus, the known beneficial effect of regular exercise training may involve an anti-inflammatory aspect, with improved mitochondrial function leading to improved fatty acid oxidation and a decrease in the synergizing effect of FFA macrophages in SM.

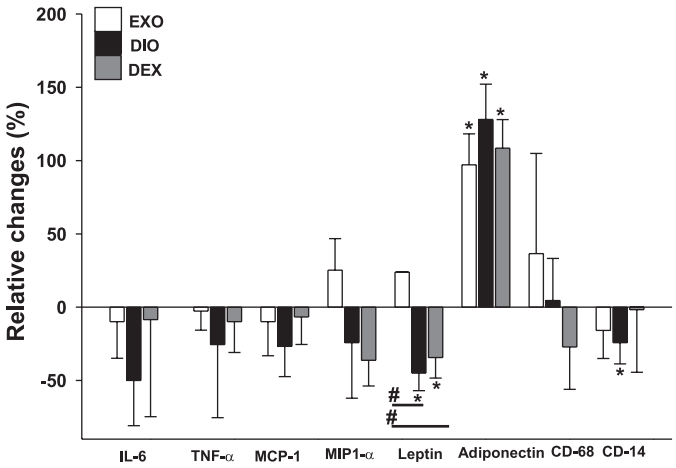


Fig. 4. Changes in adipose tissue (AT) expression of adipokines. Relative changes in AT expression of IL-6, TNF-α, MIP-1α, MCP-1, adiponectin, leptin, CD-68, and CD-14 after 12 wk in EXO, DIO, and DEX. *$P < 0.01$ compared with baseline. # $P < 0.01$ vs. changes in EXO.

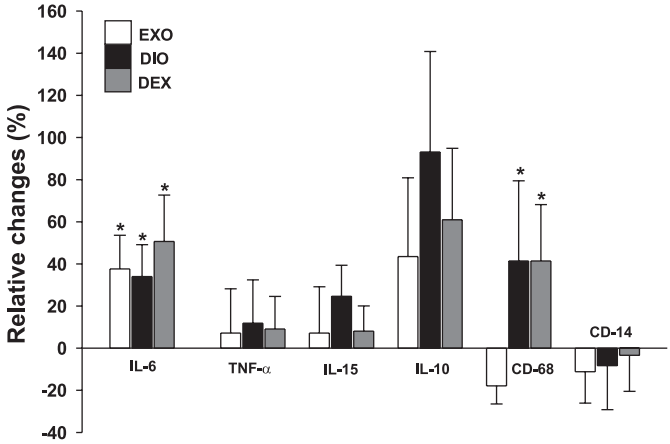


Fig. 5. Changes after 12 wk in skeletal muscle (SM) expression of IL-6, IL-15, TNF-α, and IL-10. Relative changes in SM after 12 wk in IL-6, IL-15, TNF-α, IL-10, CD-68, and CD-14 after 12 wk in EXO, DIO, and DEX. *$P < 0.05$ vs. baseline.

It has previously been shown that exercise training reduces the inflammatory process in skeletal muscle (23, 45), perhaps through a local downregulation of TNF-α in SM which is known to affect insulin resistance via two major mechanisms, inhibition of insulin receptor signaling and downregulation of GLUT4 (24). In the present study, we found a general but nonsignificant increase in all the inflammatory markers (Fig. 5). The reason for the discrepancies between our findings and others' may be partly explained by differences in the subjects included in the studies. Subjects in the present study were obese but, as mentioned, metabolically rather healthy, whereas in studies showing an exercise-induced anti-inflammatory effect in SM the subjects had more metabolic diseases like type 2 diabetes (45), were frail or elderly, or had chronic heart failure (21, 34).

We found no sex-specific differences of exercise and diet-induced weight loss on metabolic factors or inflammatory state, indicating that females and males respond similarly to these interventions.

A major strength in this study was the use of a randomized design including males and females, carefully monitored diet of all subjects, and the supervised exercise session. The inclusion of samples from blood, AT, and SM to analyze the effect of exercise on the systemic inflammatory profile is also a strength of the study. Concerning limitations it is not known whether the gene expression of the measured adipokines/myokines reflects the protein level. In conclusion, we found that only relatively large weight losses and not exercise training improved circulating markers of inflammation in these obese subjects. Moreover, we found no indication of an exercise-induced anti-inflammatory effect in skeletal muscle tissue. Thus, the exercise-induced improved metabolic function seems to be dissociated from any effect on inflammatory markers. This is in contrast to diet-induced weight loss, which improves both metabolic risk factors and the inflammatory profile in the circulation.

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## DISCLOSURES

No conflicts of interest are reported by the author(s).

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