Effects of long-term exercise and diet intervention on plasma adipokine concentrations


ABSTRACT

Background: In a randomized, controlled, 2 × 2 factorial trial on the effect of long-term changes in diet and exercise, a significant reduction in body weight and fat mass was observed. Alterations in leptin and plasminogen activator inhibitor-1 concentrations were previously reported from this study.

Objective: We examined the separate and combined effects of a 1-y exercise and diet intervention on several adipokines; adiponectin, interleukin-6 and -8, tumor necrosis factor-α, monocyte chemotractant protein-1, hepatocyte growth factor, nerve growth factor, C-reactive protein, and resistin.

Design: One hundred eighty-eight men with several risk factors for diabetes and cardiovascular disease were randomly allocated to 4 groups: diet, exercise, combined diet and exercise, and control.

Results: Plasma adiponectin concentrations remained unchanged, whereas body mass index and fat mass decreased after dietary changes and an increase in physical activity. In the control group, adiponectin concentrations were reduced. Analyzed according to the factorial design, only diet intervention had a significant (P = 0.03) positive effect on plasma adiponectin relative to control, and this effect was largely explained by changes in fat mass. After adjustment for change in percentage body fat, there were significant positive effects on tumor necrosis factor-α in all 3 intervention groups (P = 0.01 for the diet group, 0.03 for the exercise group, and 0.05 for the combined diet and exercise group). Minor changes were observed for the other adipokines. Neither baseline concentrations of nor changes in adiponectin and plasminogen activator inhibitor-1 were significantly correlated to the other adipokines, whereas concentrations of and changes in the other adipokines were significantly correlated.

Conclusion: Diet intervention had a significant positive effect on adiponectin concentrations, which is largely explained by a reduction in fat mass. Am J Clin Nutr 2007;86:1293–301.

KEY WORDS Adipokines, adiponectin, diet, exercise

INTRODUCTION

Adipose tissue is an active endocrine organ that expresses and secretes >50 metabolically active factors, termed adipokines. Adipokines are involved in several processes, such as inflammation, regulation of energy balance and appetite, insulin sensitivity, vascular hemostasis, lipid metabolism, and angiogenesis. Obesity includes a chronic low-grade inflammatory state, and high concentrations of adipokines may represent a link between expanded adipose tissue and inflammation. Adiponectin is considered the paradoxal adipokine, because its primarily beneficial properties are in relation to insulin sensitivity, inflammation, and atherogenesis. In contrast with the plasma concentrations of other adipokines, those of adiponectin have been found to be lower in subjects with obesity, type 2 diabetes mellitus, and coronary heart disease than in healthy control subjects (1–3).

In a randomized, 2 × 2 factorial trial, 188 men with several risk factors for diabetes and cardiovascular disease were randomly allocated to 4 groups: diet, exercise, a combination of diet and exercise, and control. Data on dietary intake, physical fitness, anthropometry, and plasma samples were collected before and after the intervention. During the 1-y intervention period, all 3 intervention groups lost a significantly greater amount of body fat mass than did the control group (4). In addition, blood pressure, plasma triacylglycerols, C-peptide, HDL cholesterol, and glucose metabolism, including insulin variables, were significantly and favorably improved in the intervention groups (5–8), which showed that simple intervention measures can reduce the risk of disease. Lifestyle variables such as diet and physical activity are linked to obesity, type 2 diabetes mellitus, and cardiovascular disease (5, 7–9).

1 From the Department of Nutrition, Institute of Basic Medical Sciences (MHR-A, JER, DRJ and CAD), and the Department of Biostatistics, Institute of Basic Medical Sciences (MBV), Faculty of Medicine, and the Department of Biomaterials, Institute for Clinical Dentistry, Faculty of Dentistry (JER), University of Oslo, Oslo, Norway; the Department of Sport Medicine, Norwegian School of Sport Sciences, Oslo, Norway (SAA); the Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN (DRJ); the Department of Clinical Chemistry, Ullevaal University Hospital, Oslo, Norway (PU); and the Department of Physiology and Wallenberg Laboratory, Göteborg University, Göteborg, Sweden (J-OJ).

2 Supported by grants from the Freia Chocolade Fabriks Medical Foundation, the Direktor Johan Throne Holst Foundation for Nutrition Research, the Norwegian Foundation for Health and Rehabilitation, The Research Council of Norway, the Norwegian Health Association (The Norwegian Council on Cardiovascular Diseases), the Swedish Research Council (K2007-54X-09894-16-3), the Novo Nordisk Foundation, the Swedish Strategic Foundation, and the National Institutes of Health (grant no. R01 HL 53560, to DRJ).

3 Reprints not available. Address correspondence to CA Drevon, Department of Nutrition, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, PO Box 1046 Blindern, 0316 Oslo, Norway. E-mail: c.a.drevon@medisin.uio.no.

Received April 18, 2007.

Accepted for publication July 16, 2007.
We tested the hypothesis that long-term lifestyle changes and moderate weight loss would reduce the plasma concentrations of adipokines involved in inflammation, angiogenesis, and chemotaxis and would increase adiponectin concentrations. We selected 9 adipokines: adiponectin (10), interleukin (IL)-6 (11), IL-8, monocyte chemoattractant protein-1 (MCP-1) (12), tumor necrosis factor-α (TNF-α) (13), hepatocyte growth factor (HGF) (14), nerve growth factor (NGF) (15), C-reactive protein (CRP) (16, 17), and resistin (18-20). Data on leptin (4) and plasminogen activator inhibitor-1 (PAI-1) (8) were published previously but are included here for comparison and to provide a more complete picture.

SUBJECTS AND METHODS

Study population and design

Samples and data were collected in the Oslo Diet and Exercise Study (ODES), a randomized, 2 × 2 factorial intervention trial performed in 1990 and 1991. A flow diagram of the progress of ODES is shown in Figure 1. The interventions were physical exercise, dietary change, or a combination of the 2, carried out for 1 y. The experimental design, recruitment of participants, and laboratory procedures were previously described in detail (7).

The sample in the present study comprised the 188 men who completed the ODES; they had a mean ± SD age of 45.1 ± 2.51 y old and had mildly elevated diastolic blood pressure of 88.1 ± 8.1 mm Hg, plasma HDL-cholesterol concentrations of 1.01 ± 0.16 mmol/L, triacylglycerol concentrations of 2.26 ± 1.12 mmol/L, total cholesterol of 6.33 ± 0.83 mmol/L, and body mass index (BMI; in kg/m²) of 28.6 ± 3.43 (Table 1). The baseline values for insulin, both fasting and after glucose load, were in the upper normal range, which is indicative of prediabetes (7). We used only men in our study because they were most (90%) of the eligible subjects, and metabolic differences in the few women in each group could reduce the statistical power. The participants were randomly allocated to the diet (n = 45), exercise (n = 48), combined diet and exercise (n = 58), or control (n = 37) group.

Dietary counseling was provided to participants in the diet and the combined diet and exercise groups at the start of the study and

### Table 1

<table>
<thead>
<tr>
<th>Physical and metabolic baseline characteristics in men</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>45.1 ± 2.51</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>140 ± 81.5</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.54 ± 0.62</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.33 ± 0.83</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)¹</td>
<td>1.01 ± 0.16</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)²</td>
<td>4.33 ± 0.81</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/L)</td>
<td>176 ± 206</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>2.26 ± 1.12</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>131 ± 11.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>88.1 ± 8.08</td>
</tr>
</tbody>
</table>

¹ All values are x ± SD. n = 188. Analyses were performed in fasting blood samples. There were no significant differences between the groups at baseline (one-factor ANOVA).

² n = 184.
after 3 and 9 mo. Advice was individualized and adapted according to dietary habits and risk profile. Participants were advised to increase their consumption of fish and fish products, vegetables, and fiber-rich products of complex carbohydrates and to reduce their intake of foods with high amounts of saturated fat and cholesterol. The most overweight subjects were given dietary advice to achieve weight reduction of 0.5 to 2 kg/mo. The overweight subjects were evenly distributed among the groups. After 1 y, total energy intake, energy intake from fat, and the proportion of saturated fatty acids were substantially lower among participants given dietary advice than among the control group and the exercise group.

The exercise program entailed supervised endurance exercise such as aerobics, circuit training, and fast walking or jogging, which were done 3 times/wk. The duration of each workout was 60 min. The exercise group and the combined diet and exercise group intermingled during training. The attendance of each workout was recorded, as was additional physical activity performed by some participants. Altogether, this exercise corresponded to an average of 1.8 h physical activity/wk throughout the year. The participants in the diet and control groups did not change their physical activity during the 1-y period.

All participants provided written informed consent. The ethical principles of the Helsinki Declaration were followed, and the trial was approved by the Regional Committee of Medical Ethics, eastern Norway.

Laboratory procedures

Blood samples were collected, after a 10-min period of recumbence, between 0800 and 1000 after an overnight fast and abstinence from smoking. The participants were told to abstain from vigorous exercise for 4 d before blood sampling. Each participant was examined for risk factors before and after the 1-y intervention. Body weights were measured by using a Lindel balance scale (Samhald, Klippan, Sweden) while the participants wore only underwear. Height was measured at the same time of day while the participants were barefoot. Percentage body fat (%BF) was measured by using an infrared technique (Futrex-5000; Futrex Inc, Gaithersburg, MD), which is based on near-infrared interactance as validated elsewhere (21). Subjects were seated with the forearm supported on a table, and the absorption levels were measured at the arterial midline of the right biceps muscle. Output from the Futrex-5000 device, which was programmed by the manufacturer according to their standard equation, was recorded as %BF. Intrasubject variation was 1%–2%.

Adipokine concentrations were analyzed in plasma by using enzyme-linked immunosorbent assays and radioimmunoassays and in serum by using multianalyte profiling (Luminex-100; LumineX Corporation, Austin, TX). However, both serum and plasma concentrations are referred to as plasma concentrations elsewhere in the text. Plasma adiponectin and leptin concentrations were measured by using commercially available competitive radioimmunoassays with 125I-adiponectin and 125I-leptin as tracers (Linco Research Inc, St Charles, MO). The intraassay CVs were 1.6% for adiponectin and 5.5% for leptin. The interassay CV for leptin was 3.8%, whereas no interassay CV was obtained for adiponectin because the reagents from 4 kits were pooled, and all samples were analyzed at once.

Commercially available enzyme-linked immunosorbent assay methods were used to measure plasma concentrations of IL-6 (R&D Systems, Minneapolis, MN), PAI-1 (Kabi Diagnostica, Stockholm, Sweden), resistin (Linco Research Inc) and CRP (DRG Instruments GmbH, Marburg, Germany). The intraassay CVs were 2.9% for resistin, 9.9% for CRP, and 7.0% for IL-6. Interassay CVs were 7.0% for IL-6, 12.0% for PAI-1, 5.0% and 4.9% for resistin, and 15% and 14% for CRP (low and high quality controls given for resistin and CRP).

Serum concentrations of IL-1β, IL-8, TNF-α, MCP-1, HGF, and NGF (Human serum adipokine panel B; Linco Research Inc) were simultaneously measured in the Luminex-100 system, in which the acquired fluorescence data were analyzed by using STARSTATION software (version 2.0; Applied Cytometry Systems, Sheffield, United Kingdom). All analyses were performed according to the manufacturers’ protocols. Approximately 60% of the IL-1β assays had results below the sensitivity level of the kit (0.64 pg/mL), and IL-1β was therefore excluded from the data analysis. The intraassay CVs were 6.1% for IL-8, 7.0% for TNF-α, 7.7% for MCP-1, 8.8% for HGF, and 12% for NGF. The interassay CVs (low and high quality controls, respectively) were 11% and 10% for IL-8, 17% and 11% for TNF-α, 9.0% and 7.2% for MCP-1, 9.7% and 12% for HGF, and 14% and 10% for NGF.

Statistical analysis

The data are presented as means and SDs. A natural logarithmic transformation was used except when noted, because of the skewed distribution of the adipokine data (strictly not necessary for resistin), as well as body weight and BMI. One-factor analysis of variance was used to test for differences in baseline In-transformed adipokine values among the 4 groups; no significant differences were found. Multiple regression analysis of change in adipokine concentrations were performed with ln(adipokine1 y ) as the dependent variable and with ln(adipokinebaseline) and design variables for diet, exercise, and their cross-product as independent variables. Change in %BF was included in the analysis as a covariate. We found a statistically significant diet × exercise interaction for TNF-α. We found no such effect for the other adipokines. Thus, this interaction term was removed from all the final models except TNF-α.

In the analysis according to the factorial design, diet intervention was compared with no diet intervention, and exercise intervention was compared with no exercise intervention. We studied both the cross-sectional (baseline values) and longitudinal (1-y values minus baseline values) correlations between the adipokines, as well as those between the adipokines and body weight, BMI, waist/hip ratio (WHR), %BF, and body-fat weight. Spearman’s correlation coefficients adjusted for intervention groups were determined by first assigning ranks to the values and then calculating Pearson’s partial correlation coefficients from the rank values. The reason for this adjustment is that there often are differences between groups in clinical trials. We used SPSS statistical software (version 13.0; SPSS Inc, Chicago, IL) for all analyses. A 5% level of significance was applied in all analyses—except for Figure 2 and Figure 3, where the cutoff was P < 0.01—and all P values are 2-sided. We also present 95% CIs.

RESULTS

Background data

Changes in body composition and leptin were previously published (4, 6). Body weight and BMI decreased during the 1-y
intervention in all 3 intervention groups: by 4.4% in the diet group, by 1.0% in the exercise group, and by 6.3% in the diet and exercise group (Table 2). In the control group, body weight and BMI were increased by 1.1% for both these variables. WHR and %BF decreased in all 3 intervention groups, but they remained almost unchanged in the control group.

Leptin decreased by 5% in the exercise group and by 24% in the diet and exercise group (Table 2). Analyzed according to the factorial design, significant negative effects of 21% (\(e^{-0.24}\)) of diet intervention and of 19% (\(e^{-0.21}\)) of exercise intervention were observed (Table 3). These effects were still significant, although slightly decreased, after adjustment for change in %BF (−16% for pooled diet group and −16% for pooled exercise group).

Adiponectin

A reduction of 28.5% in arithmetic mean plasma adiponectin concentrations was found in the control group, whereas those concentrations were essentially unchanged in all 3 intervention groups (Table 2). Analyzed according to the factorial design, a significant positive effect of 28% (\(e^{0.25}\) = 1.28) of diet intervention was observed on \(\ln(\text{adiponectin})\) values (\(n = 103\) in pooled diet group) (Table 3). There was no significant effect of exercise (\(n = 106\) in pooled exercise group). After adjustment for change in %BF, the effect of diet intervention remained positive but lost statistical significance.

Tumor necrosis factor-\(\alpha\)

TNF-\(\alpha\) increased by 4.1% in the diet group (Table 2) and somewhat more than that in the exercise group. However, TNF-\(\alpha\) changed less in the diet and exercise group than in the diet or exercise groups relative to the control group, which led to a significant interaction effect between diet and exercise when analysis was conducted according to the factorial design (\(P = 0.03\)). Thus, we present results for the diet, exercise, and combined diet and exercise groups compared with the control group in Table 3. After adjustment for change in %BF, there were
and BMI, and TNF-α adiponectin. CRP correlated significantly with BMI, WHR, which conceivably reflected large interindividual variations in adiponectin was not correlated with any of these variables (Table 4), (ie, body weight, BMI, WHR, %BF, and body-fat weight). Adiponectin strongly with all body-weight and body-composition measures 2. Correlations

The Spearman rank correlation coefficients for the relations between the baseline values of adipokines and body weight, BMI, WHR, %BF, and fat mass, after adjustment for the group effect, are shown in Table 4. Baseline WHR correlated significantly with leptin, IL-8, TNF-α, and CRP. Leptin correlated strongly with all body-weight and body-composition measures (ie, body weight, BMI, WHR, %BF, and body-fat weight). Adiponectin was not correlated with any of these variables (Table 4), which conceivably reflected large interindividual variations in adiponectin. CRP correlated significantly with BMI, WHR, %BF, and body-fat weight. PAI-1 correlated with body weight and BMI, and TNF-α correlated with WHR.

Spearman’s correlation coefficients for the relations between changes (1-y values minus baseline values) in adipokines and body weight, BMI, WHR, %BF, and body-fat weight, after adjustment for intervention groups, are shown in Table 5. Changes in leptin and CRP concentrations significantly and positively correlated with changes in all body-weight and body-composition measures, whereas changes in adiponectin concentrations correlated inversely with the same variables. Changes in TNF-α and HGF concentrations correlated with changes in body weight, BMI, %BF, and body-fat weight. Changes in IL-6 correlated relatively weakly with changes in body weight, BMI, WHR, and body-fat weight.

The clustering of Spearman’s correlations between baseline values of adipokines, after adjustment for intervention groups, is presented in Figure 2. Connecting lines in the figures show which adipokines are significantly correlated (cutoff: $P < 0.01$), and line thickness signifies the strength of the correlations. Baseline values of HGF, TNF-α, MCP-1, IL-8, and NGF were closely associated, whereas resistin values were more weakly associated. CRP and IL-6 were associated at baseline. Correlations between changes (1-y values minus baseline values) in adipokine concentrations are presented in Figure 3 (cutoff: $P < 0.01$). Changes in CRP, IL-6, and leptin were more closely associated with HGF, TNF-α, MCP-1, and IL-8 than at baseline. Both baseline and change values of adiponectin and PAI-1 were not significantly associated with the other adipokines studied.

**DISCUSSION**

Our main finding in the present study was that, beyond the effects on body fatness, diet or exercise intervention alone or in combination mainly had effects on adiponectin and TNF-α concentrations. As reported previously (4), there also was an effect on leptin, which reflected decreased fat mass. For the other 8 adipokines, we observed no effects or only minor effects.

The study sample included 188 men with enhanced risk of diabetes and cardiovascular disease. The interventions were well controlled and effective, and the participants in the intervention groups achieved significant improvements in several risk factors (5, 7–9). The study was conducted in the early 1990s, and unthawed aliquots of plasma and serum samples were stored at $-70 ^\circ C$.

**Adiponectin**

We found that the diet intervention had a significant positive effect on adiponectin concentrations. The effect was largely, but not completely, explained by changes in %BF. Our findings are
in accordance with those of Weiss et al (22), who reported a significant decrease in serum adiponectin in their control group but nonsignificant increases in the diet and exercise intervention groups. It is interesting that plasma adiponectin concentrations decreased considerably during 1 yr in the control group in the present study, although there was little change in BMI or fat mass. Reduction of plasma adiponectin in the control group and the small deterioration observed in variables such as fasting plasma concentrations of insulin, proinsulin, and HDL cholesterol (4) fit in with a gradual trend toward insulin resistance. Some evidence suggests that the relative proportion of large-molecular-weight adiponectin is important for insulin sensitivity (23, 24). We have measured total immunoreactive adiponectin concentration but have no estimate of the molecular distribution in the present study. Both the diet and the exercise groups showed only slightly lower concentrations of adiponectin, whereas the diet and exercise group had greater concentrations, which suggests synergic effects of the 2 interventions. When we conducted an analysis according to the factorial design, we found no significant effect of exercise on adiponectin, which confirms the findings in several other studies (25–29) and shows that exercise (which increases insulin sensitivity) without weight loss is not associated with altered adiponectin concentrations.

We found that change in %BF was significantly correlated with change in adiponectin concentrations after 1 yr. Even with consideration of this association with change in %BF in the pooled diet group, there was still an apparent effect of diet, with change in adiponectin concentrations after 1 yr. Even with a change in %BF does not appear to completely account for the effect of diet on adiponectin.

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
</table>
| Multiple regression analysis of ln(adipokine) concentration after a 1-y intervention (dependent variables), after adjustment for baseline of the dependent variable  

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Unadjusted</th>
<th>Adjusted for change in percentage body fat</th>
</tr>
</thead>
</table>
| **Leptin**  
All diet | $-0.24 (-0.33, -0.15)$ | $< 0.001$ | $-0.19 (-0.28, -0.10)$ | $< 0.001$ |
| All exercise | $-0.21 (-0.30, -0.12)$ | $< 0.001$ | $-0.17 (-0.26, -0.08)$ | $< 0.001$ |
| **Adiponectin**  
All diet | $0.25 (0.08, 0.43)$ | $0.01$ | $0.17 (-0.02, 0.35)$ | $0.07$ |
| All exercise | $0.06 (-0.12, 0.24)$ | $0.49$ | $0.01 (-0.17, 0.19)$ | $0.93$ |
| **IL-6**  
All diet | $-0.05 (-0.21, 0.12)$ | $0.58$ | $0.01 (-0.16, 0.18)$ | $0.88$ |
| All exercise | $-0.02 (-0.18, 0.15)$ | $0.86$ | $0.03 (-0.14, 0.20)$ | $0.74$ |
| **PAI-1**  
All diet | $-0.07 (-0.33, 0.19)$ | $0.59$ | $-0.42 (-0.32, 0.23)$ | $0.76$ |
| All exercise | $-0.10 (-0.37, 0.16)$ | $0.43$ | $-0.09 (-0.36, 0.18)$ | $0.53$ |
| **IL-8**  
All diet | $0.05 (-0.09, 0.19)$ | $0.49$ | $-0.02 (-0.23, 0.19)$ | $0.87$ |
| All exercise | $0.07 (-0.07, 0.21)$ | $0.34$ | $0.00 (-0.20, 0.21)$ | $0.98$ |
| **TNF-α**  
Diet only | $0.15 (0.02, 0.28)$ | $0.03$ | $0.18 (0.04, 0.32)$ | $0.01$ |
| Exercise only | $0.13 (0.00, 0.26)$ | $0.05$ | $0.15 (0.02, 0.28)$ | $0.03$ |
| Diet and exercise | $0.09 (-0.04, 0.21)$ | $0.19$ | $0.14 (0.00, 0.27)$ | $0.05$ |
| **MCP-1**  
All diet | $0.02 (-0.06, 0.09)$ | $0.64$ | $0.03 (-0.05, 0.11)$ | $0.42$ |
| All exercise | $0.04 (-0.04, 0.11)$ | $0.37$ | $0.05 (-0.03, 0.12)$ | $0.25$ |
| **HGF**  
All diet | $-0.01 (-0.12, 0.01)$ | $0.88$ | $0.04 (-0.08, 0.16)$ | $0.49$ |
| All exercise | $0.04 (-0.08, 0.16)$ | $0.50$ | $0.08 (-0.04, 0.20)$ | $0.19$ |
| **NGF**  
All diet | $0.16 (-0.09, 0.32)$ | $0.28$ | $0.15 (-0.07, 0.37)$ | $0.17$ |
| All exercise | $0.04 (-0.17, 0.25)$ | $0.74$ | $0.07 (-0.15, 0.28)$ | $0.55$ |
| **CRP**  
All diet | $-0.21 (-0.45, 0.03)$ | $0.09$ | $-0.09 (-0.33, 0.15)$ | $0.47$ |
| All exercise | $-0.08 (-0.32, 0.16)$ | $0.52$ | $0.16 (-0.22, 0.26)$ | $0.89$ |
| **Resistin**  
All diet | $-0.02 (-0.07, 0.04)$ | $0.54$ | $-0.02 (-0.08, 0.04)$ | $0.54$ |
| All exercise | $-0.01 (-0.07, 0.04)$ | $0.65$ | $-0.01 (-0.07, 0.05)$ | $0.67$ |

---

1 n = 188 men. IL, interleukin; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein-1; HGF, hepatocyte growth factor; NGF, nerve growth factor; CRP, C-reactive protein; All diet, diet interventions (diet group and diet and exercise group); All exercise, exercise interventions (exercise groups and diet and exercise group).  
2 A positive regression coefficient (b) indicates an increase.  
3 Data on leptin (4) and PAI-1 (8) were published previously.  
4 For TNF-α, the diet × exercise interaction was significant. Thus, we present results for the diet, exercise, and combined diet and exercise groups as compared with the control group.
Weight reduction, achieved via changes in diet or exercise or both (2, 30–32) or as a result of bariatric surgery (25, 33–35), may increase adiponectin concentrations, whereas several other studies have observed no significant alterations in adiponectin concentrations despite reductions in fat mass (36–40). This lack of alteration could be due to moderate weight loss, large individual variations in plasma adiponectin concentration, limited numbers of subjects, or sex differences.

**Tumor necrosis factor-α**

We were surprised to find that, after adjustment for change in %BF, all 3 interventions increased TNF-α concentrations. Despite a finding of statistical significance, we think this finding may be attributed to chance, given that the combination of diet and exercise had a smaller effect than did either diet or exercise alone. If the finding reflected a biological phenomenon, we would expect the combined intervention to have a greater effect. Several researchers report reductions in TNF-α concentrations after weight loss (29, 41–43), which is explained by reduction in fat mass, whereas others report unchanged concentrations (22, 39, 40, 44). Shahid et al (31) reported higher, but not significantly higher, TNF-α concentrations after a 19-wk diet and exercise intervention.

**Other adipokines**

We hypothesized that long-term changes in lifestyle, including significant weight loss, would reduce plasma concentrations of adipokines related to inflammation. However, when we analyzed our data in line with the factorial design, we found that only adiponectin and TNF-α responded to the interventions. One reason for this may be that our study participants were only in a very-low-grade inflammatory state (average BMI: 28.6 ± 4.4). We also found that the moderate weight loss was not sufficient to alter their circulating adipokine profiles. In a pooled analysis of 3 studies (44–46) of the effects of bariatric surgery on circulating concentrations of CRP, PAI-1, leptin, and TNF-α, Fain (47) reported

---

**TABLE 4**

Spearman’s correlation coefficients, adjusted for intervention groups, between baseline concentrations

<table>
<thead>
<tr>
<th></th>
<th>Body weight</th>
<th>BMI</th>
<th>W/H ratio</th>
<th>Percentage body fat</th>
<th>Fat mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>0.535(^2)</td>
<td>0.659(^2)</td>
<td>0.463(^2)</td>
<td>0.495(^2)</td>
<td>0.662(^2)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>−0.033</td>
<td>−0.060</td>
<td>0.015</td>
<td>−0.071</td>
<td>−0.047</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.050</td>
<td>0.081</td>
<td>0.122</td>
<td>0.146(^4)</td>
<td>0.104</td>
</tr>
<tr>
<td>PAI-1</td>
<td>0.216(^4)</td>
<td>0.188(^4)</td>
<td>0.125</td>
<td>0.044</td>
<td>0.128</td>
</tr>
<tr>
<td>IL-8</td>
<td>−0.031</td>
<td>0.048</td>
<td>0.172(^4)</td>
<td>0.077</td>
<td>0.088</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.057</td>
<td>0.111</td>
<td>0.215(^4)</td>
<td>0.093</td>
<td>0.116</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.051</td>
<td>0.080</td>
<td>0.095</td>
<td>0.004</td>
<td>0.053</td>
</tr>
<tr>
<td>HGF</td>
<td>0.120</td>
<td>0.121</td>
<td>0.128</td>
<td>0.045</td>
<td>0.110</td>
</tr>
<tr>
<td>NGF</td>
<td>−0.002</td>
<td>0.052</td>
<td>0.066</td>
<td>0.117</td>
<td>0.107</td>
</tr>
<tr>
<td>CRP</td>
<td>0.069</td>
<td>0.176(^3)</td>
<td>0.295(^3)</td>
<td>0.206(^3)</td>
<td>0.204(^3)</td>
</tr>
<tr>
<td>Resistin</td>
<td>0.009</td>
<td>−0.013</td>
<td>−0.049</td>
<td>0.041</td>
<td>0.007</td>
</tr>
</tbody>
</table>

\(^{1}\) n varies from 175 to 188 subjects. W/H, waist-to-hip; IL, interleukin; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemotactrant protein-1; HGF, hepatocyte growth factor; NGF, nerve growth factor; CRP, C-reactive protein.

\(^{2}\) P ≤ 0.01.

\(^{3}\) P ≤ 0.05.

\(^{4}\) P ≤ 0.01.

---

**TABLE 5**

Spearman’s correlation coefficients, adjusted for intervention groups, between changes (1-y concentrations minus baseline concentrations)

<table>
<thead>
<tr>
<th></th>
<th>Body weight</th>
<th>BMI</th>
<th>W/H ratio</th>
<th>Percentage body fat</th>
<th>Fat mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>0.438(^2)</td>
<td>0.435(^2)</td>
<td>0.274(^2)</td>
<td>0.256(^2)</td>
<td>0.357(^2)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>−0.289(^2)</td>
<td>−0.294(^2)</td>
<td>−0.246(^2)</td>
<td>−0.299(^2)</td>
<td>−0.318(^2)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.191(^3)</td>
<td>0.187(^3)</td>
<td>0.149(^3)</td>
<td>0.136</td>
<td>0.169(^4)</td>
</tr>
<tr>
<td>PAI-1</td>
<td>0.080</td>
<td>0.078</td>
<td>0.087</td>
<td>−0.008</td>
<td>0.018</td>
</tr>
<tr>
<td>IL-8</td>
<td>−0.005</td>
<td>0.002</td>
<td>−0.022</td>
<td>−0.005</td>
<td>−0.005</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.189(^4)</td>
<td>0.192(^4)</td>
<td>0.047</td>
<td>0.177(^4)</td>
<td>0.216(^4)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.066</td>
<td>0.068</td>
<td>0.024</td>
<td>0.052</td>
<td>0.075</td>
</tr>
<tr>
<td>HGF</td>
<td>0.269(^2)</td>
<td>0.278</td>
<td>0.068</td>
<td>0.179(^4)</td>
<td>0.240(^4)</td>
</tr>
<tr>
<td>NGF</td>
<td>0.096</td>
<td>0.096</td>
<td>0.031</td>
<td>0.070</td>
<td>0.100</td>
</tr>
<tr>
<td>CRP</td>
<td>0.241(^2)</td>
<td>0.238(^3)</td>
<td>0.182(^4)</td>
<td>0.176(^4)</td>
<td>0.220(^4)</td>
</tr>
<tr>
<td>Resistin</td>
<td>0.013</td>
<td>0.016</td>
<td>−0.031</td>
<td>−0.008</td>
<td>−0.014</td>
</tr>
</tbody>
</table>

\(^{1}\) n varies from 175 to 188 subjects. W/H, waist-to-hip; IL, interleukin; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemotactrant protein-1; HGF, hepatocyte growth factor; NGF, nerve growth factor; CRP, C-reactive protein.

\(^{2}\) P ≤ 0.001.

\(^{3}\) P ≤ 0.05.

\(^{4}\) P ≤ 0.01.
that, even with dramatic weight loss (mean BMI reduced from 45 to 33), there were only minimal reductions in TNF-α and IL-6 concentrations. Considering that the average weight loss in our subjects was much more modest, it is not surprising that we do not see reduced concentrations of those variables. CRP, PAI-1, and leptin were more responsive in the bariatric surgery patients and decreased in response to the reduction in BMI (47). In the present study, there was a tendency for CRP to decrease only during the dietary intervention. Our finding that resistin concentrations were unaltered in response to lifestyle changes is consistent with findings of several other studies (31, 32, 40, 48), although there are some conflicting results (49).

**Correlations**

Adiponectin and PAI-1 stand out because their baseline concentrations and changes were not associated with each other or with any of the other adipokines (cutoff: *P* < 0.01). This correlation structure suggests that their concentrations are regulated via pathways that are distinct from each other and from the pathways of other adipokines. Baseline adiponectin correlated poorly with body weight, BMI, WHR, %BF, and fat mass, which probably reflects the large biological variation. The changes in adiponectin concentrations, however, correlated negatively with these variables, as expected.

IL-6 is a well-known inducer of CRP production in the liver (50), and the associations of these factors with each other at baseline as well as prospectively were expected. Both baseline concentrations and changes during intervention in IL-8, MCP-1, HGF, NGF, and TNF-α were closely associated, which suggested mutually related pathways. Nevertheless, pathways within this metabolically related cluster of adipokines may have considerable variation, given that no correlation coefficients >0.55 were observed.

**Conclusions**

Our results provide new information on the effect of long-term lifestyle changes on a broad range of adipokines. We showed that a loss of fat mass (body weight) largely explains the positive effect of diet on adiponectin plasma concentrations. Plasma concentrations of adiponectin appear to be regulated through pathways different from those for other adipokines. After adjustment for change in %BF, we found that all 3 interventions increased TNF-α concentrations, which was opposite the expected finding.

We thank AR Engert for excellent technical assistance. The authors’ responsibilities were as follows—SAA, PU, and CAD: provided plasma and serum from the Oslo Diet and Exercise Study; MHR-A, DRJ, JER, and CAD: formulated the study strategy; MHR-A: conducted the interleukin-8, tumor necrosis factor-α, monocyte chemoattractant protein-1, hepatocyte growth factor, nerve growth factor, C-reactive protein, and resistin analyses; JER: conducted the adiponectin analyses; J-OJ: conducted the interleukin-6 analyses; MHR-A: carried out the statistical analyses; MBV, DRJ, and CAD: supervised the statistical analyses; MHR-A and CAD: wrote the manuscript; and all authors: contributed to revision of the manuscript. None of the authors had a personal or financial conflict of interest.

**REFERENCES**


44. Kopp HP, Kopp CW, Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm 2006;74:443–77.
47. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm 2006;74:443–77.