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Exercise reduces plasma levels of the chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome

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Aims Inflammation plays an essential role in the atherosclerotic process, and chemokines such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) seem to play a pivotal role in the pathogenesis of atherosclerosis. A possible common inflammatory basis for the pathogenesis of type 2 diabetes, metabolic syndrome and atherosclerosis has been suggested. In this study we investigated the effect of physical exercise and the HMG-CoA reductase inhibitor pravastatin on peripheral markers of inflammation in subjects with the metabolic syndrome.
Methods The study was an unmasked randomized 2×2 factorial trial of 12 weeks duration.
Results In the combined exercise groups there was a significant reduction in MCP-1 and IL-8 of 48 pg/ml (P=0.04) and 1.0 pg/ml (P=0.007), respectively, as compared to the combined non-exercise groups. There was also a significant reduction vs baseline of 50 pg/ml (33%) (P=0.002) and 0.35 pg/ml (13%) (P=0.03) for MCP-1 and IL-8, respectively. Changes in MCP-1 were significantly correlated to changes in visceral fat (r=0.41, P=0.02).
Conclusion The protective effect of exercise might in part be due to suppression of the inflammatory process.

Introduction

The metabolic syndrome, or the insulin resistance syndrome, is a common precursor to type 2 diabetes. It is characterized by the simultaneous presence of several cardiovascular risk factors, including abdominal obesity,

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Table 1 Baseline characteristics in the four groups of individuals with the metabolic syndrome

	Control (*n*=6)	Pravastatin (*n*=8)	Exercise (*n*=9)	Pravastatin and exercise (*n*=9)
Age (years)	46 (44–56)	55 (47–62)	42 (40–52)	45 (41–59)
Fasting glucose (mmol/l)	7.5 (5.8–9.0)	7.9 (6.7–10.5)	6.8 (6.2–8.0)	7.2 (6.0–9.6)
VO2 (ml/kg/min)	22 (21–26)	20 (16–25)	21 (16–25)	21 (20–24)
Waist circumference (cm)	108 (106–118)	113 (108–122)	120 (112–126)	117 (112–125)
Systolic blood pressure (mmHg)	143 (140–150)	153 (148–159)	142 (140–152)	144 (142–148)
Diastolic blood pressure (mmHg)	91 (90–95)	92 (87–95)	92 (90–92)	96 (92–96)
Triglycerides (mmol/l)	2.4 (1.3–4.2)	1.9 (1.3–2.4)	2.3 (1.3–2.7)	2.5 (2.0–2.7)
HDL cholesterol (mmol/l)	0.9 (0.9–1.0)	1.0 (0.9–1.4)	1.0 (0.8–1.1)	1.0 (0.9–1.2)
BMI (kg/m^2)	31 (29–31)	31 (29–33)	36 (30–38)	33 (32–33)
Subjects with diabetes mellitus (*n*)	5	6	5	5

Data as median and 25–75% interquartile range. VO2=oxygen consumption; HDL=high density lipoprotein; BMI=body mass index.

dyslipidaemia (elevated triglycerides, low HDL cholesterol), hypertension and insulin resistance in the presence or absence of overt glucose intolerance.[1] Type 2 diabetes is recognised as a major cardiovascular risk factor,[2] and is associated with increased frequency of conventional risk factors for cardiovascular disease.[3] The metabolic syndrome, which is much more prevalent than type 2 diabetes, is also considered a major risk factor in recent guidelines.[1]

It has gradually become evident that inflammation plays an essential role in atherosclerosis. Leukocyte infiltration into the vascular wall is involved in virtually all stages of the process, from the fatty streak to the complex atheromatous plaque.[4] Increasing evidence suggests that chemokines, such as interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1), play an important role in this process, in part by attracting mononuclear cells to the arterial wall.[5] Moreover, C-reactive protein (CRP) has been identified as a negative prognostic factor for the development of coronary heart disease both in healthy individuals[6,7] and in subjects with the metabolic syndrome,[8] and plasma levels of CRP may be modified by HMG-CoA reductase inhibitors (statins), independent of the LDL-lowering effect of these drugs.[9] Furthermore, complement activation seems to be involved in both initiation and progression of atherosclerosis.[10] Indeed, some investigators have pointed out that both type 2 diabetes, metabolic syndrome and atherosclerosis are multifactorial conditions which appear to have a common inflammatory basis.[11]

Adipose tissue is metabolically active and secretes various chemokines[12] and proinflammatory cytokines such as interleukin-6 (IL-6)[13] and tumour necrosis factor-α (TNF-α).[14] Endurance training[15] and strength training[16] have both been shown to decrease the amount of visceral fat, and endurance training has beneficial effect on several components of the metabolic syndrome.[17] Given that a combination of endurance training and strength training will decrease the amount of visceral fat, we sought to determine the effects of such exercise on plasma levels of several inflammatory mediators and on the components of the metabolic syndrome. Pravastatin was used for comparison, because of its documented anti-inflammatory effects.[9,18]

Methods

Experimental design and participants

The study was an unmasked randomized 2×2 factorial trial of 3 months duration. The participants were recruited after an advertisement in the local newspaper. The inclusion criteria were: men aged 20–75 years with the metabolic syndrome (as defined in ref.[1]), physically inactive (<30 min of physical activity per day) and with central obesity (as central obesity is not mandatory for the definition of the metabolic syndrome but of particular interest in this study, a waist circumference >90 cm, which is associated with increased cardiovascular risk,[19] was defined as the cut-off). Individuals with known heart disease were excluded. Those treated with statins were either excluded, or, for four subjects where it was considered medically safe, statins were washed out during a period of 4 weeks and the persons included.

During a period of 2 months, 34 participants were selected out of a total of 110 screened. Baseline characteristics are shown in Table 1. It should be noted that 21 of the participants had diabetes. The participants were randomized into one of four groups: control (group C, *n*=6), exercise only (group E, *n*=9), pravastatin only (group P, *n*=9) or the combination of pravastatin and exercise (group PE, *n*=10). Written informed consent was obtained.

Data were obtained at randomization and after 12 weeks. Two of the participants, one in group P and one in PE, were withdrawn from the study due to side effects; muscle soreness and elevation of creatine kinase, respectively. As the study was not performed on an intention-to-treat basis, data from these two participants were excluded from statistical analysis.

The study was approved by the regional ethics committee and conformed with the principles outlined in the Declaration of Helsinki.

The intervention programme

The exercise programme consisted of endurance type of exercise, such as walking/jogging on treadmill, and strength training. Workouts were performed three times a week in a training

Table 2 The changes from baseline in selected variables in subjects with the metabolic syndrome

	Combined exercise group (n=18)	Combined non-exercise group (n=14)
VO2 (ml/kg/min)	3.1 (1.4–4.6)[a,b]	−1.5 (−4.0–2.2)
Waist circumference (cm)	−7.5 (−11 to −3.0)[a,b]	1.0 (−4.0–5.0)
BMI (kg/m^2)	−0.7 (−1.7–0) [a,b]	0.5 (0–0.6)
Systolic blood pressure (mmHg)	−5.0 (−12 to −2.0) [a,b]	1.0 (−6.0–8.0)
Diastolic blood pressure (mmHg)	−4.0 (−8.0–0)[b]	0 (−4.0–2.0)
Glucose (mmol/l)	−0.5 (−1.1 to −0.2)[b]	0 (−0.9–0.5)
HbA1c (%)	−0.2 (−0.6–0)[b]	0 (−0.3–0.1)

Data as median and 25–75% interquartile range. Combined exercise group consists of group E (exercise only) and group PE (pravastatin and exercise); combined non-exercise group consists of group P (pravastatin only) and group C (control). VO2=oxygen consumption; BMI=body mass index.

[a] P<0.05 vs combined non-exercise groups.
[b] P<0.05 vs baseline. For accurate P-values see text.

studio, mostly in supervised groups. The duration of each workout was 45–60 min. Approximately 40% of the scheduled workout was walking/jogging/cycling and 60% was strength training. The strength training was performed in cycles with 15–20 repetitions per cycle, and large muscle groups such as thighs, back and abdomen were trained. The participants were encouraged to record the training in logs.

Participants in the pravastatin group received 40 mg pravastatin per day, a dosage known to exert anti-inflammatory effects in vivo,[9] as well as clinical benefit in both primary[20] and secondary[21,22] prevention of coronary heart disease. Groups E and PE were not separated during physical exercise. Participants in groups C and P were encouraged not to change their life style during the intervention period.

Laboratory procedures

Blood pressure was measured in the sitting position after 5 min rest. Three recordings were made, and the mean of the last two measurements was used for statistical analysis.

Oxygen uptake was measured during walking/jogging on a treadmill at the same heart rate at baseline and after intervention to obtain appropriate comparability. This target heart rate was defined as 80% of maximum, estimated from the equation 220–age (years). Five recordings were made at the target frequency, and the median was used for statistical analysis. The expired air was analysed using a SensorMedics system. Gas analysers were calibrated before each test.

Computerized tomography (CT) scans were performed on a General Electric Pace Plus scanner using validated procedures.[23] The scans were performed at 120 kV. The subjects were examined in supine position with their arms stretched above their head. To minimize the amount of radiation, the CT scans were performed at only one site: at the level corresponding to the disk between the 2nd and the 3rd lumbar vertebrae. In men, this single scan has showed a higher correlation with visceral adipose tissue volume determined by multiple scans than any other single scan.[23] In order to obtain high accuracy and reproducibility for the measurements, a scout view was used to establish the position of the scans to the nearest 2 mm. The attenuation interval for adipose tissue calculations was −30 to −190 Hounsfield units. Subcutaneous and visceral fat were calculated by delineating their respective areas with a graph pen. All CT scans were examined at the end of the study and the radiologist was blinded to the randomization.

Blood samples were collected between 8 and 10 a.m. after an overnight fast. To minimize the influence of any incidental acute phase reaction, participants were requested not to perform any major physical activity the last 5 days before collections of blood samples. Furthermore, in two individuals sampling was delayed for 2–3 weeks due to minor infection.

Routine blood analyses were performed in the hospital laboratory using standard equipment and assays. Blood, serum and plasma for analysis of HbA1c, C-peptide, high sensitivity CRP, complement activation products, interleukins, MCP-1 and TNF-a were frozen in aliquots at −70 °C and analysed in parallel at the end of the study. The complement activation products C3bc and TCC (terminal SC5b-9 complement complex) were quantified in ELISA assays as previously described.[24] Interleukins 6, 8 and 10 and TNF-α were analysed using PeliKine Compact EIA kits (CLB, Amsterdam, The Netherlands). MCP-1 was determined by EIA with the Duoset from R&D Systems (Minneapolis, MN), according to the manufacturer's instructions.

Statistics

Non-parametric tests were used for statistical analyses. The 2×2 factorial design was used to compare the combined exercise group E+PE with the combined non-exercise group C+P, and the combined pravastatin group P+PE with the combined non-pravastatin group C+E. Changes from baseline were evaluated in the combined exercise group E+PE and in the combined pravastatin group P+PE, respectively. Inter-group comparisons were evaluated using the Mann–Whitney U test. Wilcoxon's test for paired observations was used to evaluate changes from baseline within the combined intervention groups. Spearman correlation was used for regression analyses. The chosen significance level was a two-tailed P<0.05.

Results

Anthropometry and physiology

The results are presented in Table 2. In the combined exercise group E+PE, there was a significant increase in exercising oxygen consumption (at 80% of estimated maximum heart rate) with a median of 4.6 ml/kg per minute (P=0.007) vs the combined non-exercise group C+P, and of 3.1 ml/kg per minute vs baseline (P=0.0006). In the combined exercise group, waist circumference decreased with a median of 8.5 cm (P=0.0001) vs the combined non-exercise group, and 7.5 cm (P=0.0004) vs

Table 3 The changes from baseline in lipid parameters in subjects with the metabolic syndrome

	Combined pravastatin group (*n*=17)	Combined non-pravastatin group (*n*=15)
Cholesterol (mmol/l)	−1.2(−1.9to−0.6)[a,b]	0.1(−0.5–0.5)
LDL (mmol/l)	−1.2(−1.5to−0.7)[a,b]	0 (−0.2–0.5)

Data as median and 25–75% interquartile range. Combined pravastatin group consists of group P (pravastatin only) and group PE (pravastatin and exercise); combined non-pravastatin group consists of group E (exercise only) and group C (control). LDL=low density lipoprotein.

[a] *P*<0.05 vs combined non-pravastatin groups.
[b] *P*<0.05 vs baseline. For accurate *P*-values see text.

Table 4 The changes from baseline in plasma levels of chemokines in subjects with the metabolic syndrome.

(a)	Combined exercise group (*n*=18)	Combined non-exercise group (*n*=14)
IL-8 (pg/l)	−0.35 (−3.4–0)[a,b]	0.65 (−0.1–1.6)
MCP-1 (pg/l)	−50 (−93 to −26)[a,b]	−2.0 (−46–11)
(b)	Combined pravastatin group (*n*=17)	Combined non-pravastatin group (*n*=15)
IL-8 (pg/l)	0 (−1.1–0.9)	−0.1 (−2.0–0.6)
MCP-1 (pg/l)	−33 (−93 to −6.0)[b]	−46 (−55–4.0)

Data as median and 25–75% interquartile range. (a) Combined exercise group consists of group E (exercise only) and group PE (pravastatin and exercise); combined non-exercise group consists of group P (pravastatin only) and group C (control). (b) Combined pravastatin group consists of group P (pravastatin only) and group PE (pravastatin and exercise); combined non-pravastatin group consists of group E (exercise only) and group C (control). IL-8=interleukin 8; MCP-1=monocyte chemoattractant protein-1.

[a] *P*<0.05 vs combined non-exercise groups.
[b] *P*<0.05 vs baseline. For accurate *P*-values see text.

baseline. Systolic blood pressure was reduced in the combined exercise group with a median of 6 mmHg (*P*=0.01) vs the combined non-exercise groups and 5 mmHg (*P*=0.0005) vs baseline. Diastolic blood pressure was reduced in the combined exercise group with a median of 4 mmHg (*P*=0.003) vs baseline, and there was a trend towards decrease of 4 mmHg (*P*=0.05) vs the combined non-exercise groups. Body mass index was decreased in the combined exercise group with a median of 1.2 kg/m^2 (*P*=0.002) as compared to the combined non-exercise group, and 0.7 kg/m^2 (*P*=0.01) vs baseline.

Glucose metabolism

The results are presented in Table 2. There were no significant inter-group differences, but some intra-group changes were observed. HbA1c was reduced in the combined exercise group E+PE with a median of 0.2% in absolute value (*P*=0.01 vs baseline, *P*=0.19 vs combined non-exercise group C+P). Fasting glucose was reduced in the combined exercise group E+PE with a median of 0.5 mmol/l (*P*=0.004 vs baseline, *P*=0.28 vs. combined non-exercise group C+P).

Lipids

The results are presented in Table 3. Pravastatin significantly reduced total cholesterol and LDL-cholesterol, whereas HDL-cholesterol and triglycerides were not affected. In the combined pravastatin group P+PE, cholesterol was reduced with a median of 1.3 mmol/l as compared to the combined non-pravastatin group C+E (*P*=0.0001) and 1.2 mmol/l vs baseline (*P*=0.001). In the combined pravastatin group, LDL-cholesterol was reduced with a median of 1.2 mmol/l as compared to the combined non-pravastatin group C+E (*P*=0.00002) and vs baseline (*P*=0.001).

Inflammation

The results from the combined groups are presented in Table 4 and Table 5, whereas results from the individual groups are presented in Fig. 1. In the combined exercise group E+PE there was a significant reduction in MCP-1 and IL-8 of 48 pg/ml (*P*=0.04) and 1.0 pg/ml (*P*=0.007), respectively, as compared to the combined non-exercise group P+C. There was also a significant reduction vs baseline of 50 pg/ml (33%) (*P*=0.002) and 0.35 pg/ml (13%) (*P*=0.03) for MCP-1 and IL-8, respectively. In the combined pravastatin group P+PE, MCP-1 was reduced vs. baseline with a median of 33 pg/ml (22%) (*P*=0.005), but there was no significant difference as compared to the combined non-pravastatin group C+E.

When examining the whole study population regardless of intervention, changes in MCP-1 were positively correlated to changes in visceral fat (*r*=0.41, *P*=0.02) (Fig. 2), whereas no significant correlation was found to changes in subcutaneous fat. Changes in IL-8 were also

Table 5 Spearman rank coefficients and p-values (in parentheses) between changes in chemokines and selected variables for all subjects (n=32), irrespective of intervention group

	δIL-8	δMCP-1
δVisceral fat	0.28 (0.16)	0.41 (0.02)[a]
δSubcutaneous fat	0.03 (0.87)	0.13 (0.47)
δVO2	−0.22 (0.22)	−0.11 (0.54)

See Table 1 and Table 3 for explanation of abbreviations.

[a]Statistically significant.

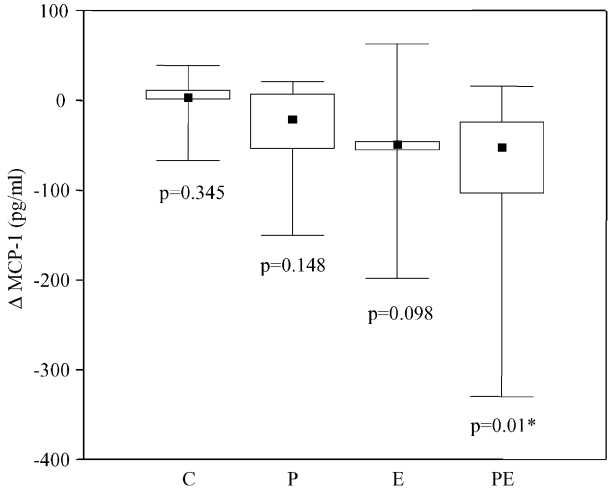

Fig. 1 Changes (δ) in plasma levels of MCP-1 from baseline in subjects with the metabolic syndrome after 12 weeks of intervention. The participants were divided into the following groups: C=control (n=6), P=pravastatin (n=8), E=exercise (n=9), PE=pravastatin and exercise (n=9). Median, 25/75% interquartile range and total range are indicated. P values indicate change vs baseline.

more positively correlated to changes in visceral fat than to changes in subcutaneous fat. Changes in MCP-1 and IL-8 were negatively but not significantly correlated to changes in oxygen consumption during exercise.

There were no significant changes in the levels of chemokines or cytokines in the control group. No significant changes were observed for CRP, TNF-α, IL-6, IL-10 or complement activation products in either of the groups (P>0.10).

Discussion

In this study we investigated the effect of exercise on inflammatory parameters in subjects with the metabolic syndrome. In the combined exercise group E+PE, we observed a statistically significant reduction in both MCP-1 and IL-8 as compared to the combined non-exercise group C+P, and from baseline to end of the observation period.

Strenuous exercise can increase plasma levels of various chemokines and cytokines, including IL-8, IL-6 and TNF-α in healthy individuals.[25] However, epidemiological

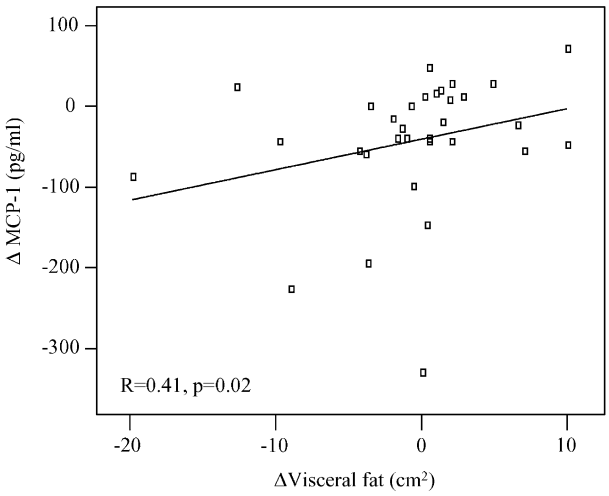

Fig. 2 Spearman correlation plot between changes in visceral fat (abscissa) and MCP-1 (ordinate) for all subjects (n=32), irrespective of intervention group (see legend to Fig. 1). r=0.41, P=0.02.

studies have shown that increasing levels of physical activity are associated with reduced levels of CRP in healthy subjects.[26,27] Furthermore, in patients with heart failure, who have increased plasma levels of chemokines,[28] it has been reported that modest exercise can reduce peripheral markers of inflammation, among them MCP-1.[29] To our best knowledge, our data are the first to show that this also applies to subjects with the metabolic syndrome.

Plasma levels of MCP-1 were also significantly reduced vs. baseline in the combined pravastatin group P+PE. We have recently demonstrated that simvastatin and atorvastatin can reduce gene expression of several chemokines and chemokine receptors in patients with coronary artery disease, although plasma levels of MCP-1 were not reduced.[30] Inhibition of MCP-1 synthesis by statins in vitro has previously been reported.[31] To our knowledge, the present study is the first to indicate that statins may decrease plasma levels of MCP-1 in vivo. However, this decrease may in part be a result of the fact that half of the subjects exercised. This notion is supported by the fact that there was no statistically significant difference between the combined pravastatin group P+PE and the combined non-pravastatin group E+C regarding MCP-1. The more extensive lowering of MCP-1 in group PE than in groups E and P (Fig. 1) suggests an additive, suppressive effect of pravastatin and exercise on plasma levels of MCP-1 and further studies with larger groups are warranted to elucidate these relations.

From our data, pravastatin did not seem to affect plasma levels of IL-8. The reduction in the combined exercise group E+EP is therefore most likely caused by exercise alone. A reduction in plasma IL-8 by exercise has to our knowledge previously not been demonstrated.

The association between inflammation and atherosclerosis is well established. In fact, chemokines seem to play a pivotal role in the pathogenesis of atherosclerosis,

in part by attracting mononuclear cells to the vessel wall.[5] Knockout-mice lacking MCP-1 or IL-8 or their corresponding receptors have significantly reduced progression of atherosclerosis.[32] MCP-1 and IL-8 have been reported to trigger the firm adhesion of monocytes to vascular endothelium under flow conditions.[33] MCP-1 is also involved in the activation of macrophages in the atheromatous plaque, and plasma levels are elevated in patients with acute myocardial infarction and unstable angina, but not in those with stable angina.[34] Furthermore, elevated plasma levels of MCP-1 have recently been found to be associated with increased risk of death or myocardial infarction in patients with acute coronary syndromes, and has been identified as a potential therapeutic target.[35] Thus, in light of our findings, the beneficial effect of exercise in regard to cardiovascular mortality[36] might at least in part be due to reduction in MCP-1.

Several studies have provided support for the hypothesis that insulin resistance may be associated with chronic subclinical inflammation. High glucose concentrations have been found to induce the release of IL-8 in endothelial and smooth muscle cells, giving one possible explanation for the link between hyperglycaemia, inflammation and atherosclerosis.[37] CRP, IL-6 and TNF-α have been shown to be elevated in association with quantitative measures of insulin resistance.[38] Adipose tissue is metabolically active and pre-adipocytes have been reported to secrete both MCP-1 and IL-8.[12]

It seems from our data as if the reduction in chemokines, especially MCP-1, is more correlated to a reduction in visceral fat than to a reduction in subcutaneous fat or increased oxygen consumption (Fig. 2). Although visceral fat did not decrease significantly in the exercise groups, the reduction in especially MCP-1 was significantly correlated to a reduction in visceral fat, irrespective of intervention group, indicating that the reduction in visceral fat, rather than the intervention itself, might influence the plasma levels of chemokines. Whether visceral fat exerts a direct inflammatory effect or whether other mechanisms are involved remains unclear. Both MCP-1 and IL-8 are produced in, and secreted by, endothelial cells, and the production is stimulated by mechanical stretch.[39] Thus, improved vascular function due to exercise[40] might in part explain the inhibitory effect on chemokines.

One limitation of our report is the sample size due to the small population in the city where the study was conducted. This will increase the risk of statistically false negative results (type II errors), whereas false positive results (type I errors) are less likely. Thus, we suggest that the data for MCP-1 and IL-8 are the most reliable data obtained in this study. Another limitation of this study is the fact that the control group may have exercised in spite of encouragements not to do so. However, a lack of change in VO2, abdominal circumference, blood pressure and glycaemic control in this group makes this less likely. Moreover, if such unintended exercise really did take place, the statistically significant differences observed between the exercise- and non-exercise groups would be an underestimate rather than an overestimate and in fact underscores the observations. On the other hand, exercise may not have been the only difference between the intervention groups. As the exercise groups, in contrast to the control group and pravastatin group, met on a regular basis, discussions regarding lifestyle changes such as diet may have taken place. The significant reduction in abdominal circumference despite no significant reduction in visceral fat, could have been caused by reduced bowel content due to unintended changes in diet, but may as well be a result of improved bowel function induced by exercise.

Lifestyle changes, including exercise, have been found to reduce the risk of developing diabetes mellitus,[41] and physical inactivity is an important risk factor for both cardiovascular death and all cause mortality.[42] Inflammation seems to be involved in the pathogenesis of both diabetes mellitus and atherosclerosis. Our findings suggest an anti-inflammatory effect of exercise through reduced plasma levels of chemokines. The protective effect of exercise might in part be due to suppression of the inflammatory process.

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MT, KTL, TC and TEM developed the study protocol. MT was the principal investigator. KTL and TEM were responsible for analysis of cytokines and complement activation products. JKD was responsible for analysis of chemokines. LM contributed with statistical analysis. RB was responsible for quantification of visceral and subcutaneous fat on computerized tomography. All co-authors participated in the writing of the manuscript.

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