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ORIGINAL ARTICLE

Short-term treatment with ezetimibe, simvastatin or their combination does not alter circulating adiponectin, resistin or leptin levels in healthy men

Ioanna Gouni-Berthold*, Heiner K. Berthold†, John P. Chamberland‡, Wilhelm Krone* and Christos S. Mantzoros‡

**Department of Internal Medicine II, University of Cologne, Cologne, Germany, †Medical Faculty of the University of Bonn, Bonn, Germany and ‡Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*

Summary

Objective Statin therapy decreases cardiovascular morbidity and mortality, and ezetimibe, a novel cholesterol absorption inhibitor has both lipid-lowering and anti-atherosclerotic effects in animal models. As several adipokines, that is, adiponectin, high molecular weight (HMW) adiponectin, leptin and/or possibly resistin are involved in the pathogenesis of insulin resistance (IR), dyslipidaemia and atherosclerosis, we investigated whether ezetimibe and/or statin treatment may modulate serum concentrations of these four major adipokines.

Research design and methods One-centre, randomized, parallel three-group study in 72 healthy men [mean age 32 ± 9 years, mean body mass index (BMI) 25·7 ± 3·2 kg/m^2].

Patients Seventy-two healthy men. Each group of 24 subjects received a 14-day treatment with either ezetimibe (10 mg/day), simvastatin (40 mg/day) or their combination. Blood was drawn before and after the 14-day treatment period.

Measurements Lipid levels, IR indices, serum leptin, adiponectin, HMW adiponectin and resistin concentrations.

Results Neither ezetimibe nor simvastatin or their combination had any effect on serum leptin, adiponectin, HMW adiponectin and resistin concentrations. Baseline leptin levels correlated positively, while adiponectin and HMW adiponectin negatively, with BMI. Leptin concentrations correlated negatively while adiponectin and HMW adiponectin positively with plasma high-density lipoprotein-cholesterol concentrations. Resistin concentrations were not associated with BMI, lipid levels or indicators of IR.

Conclusions Treatment with ezetimibe, simvastatin or their combination does not alter circulating levels of adiponectin, leptin or resistin in adult healthy men.

Correspondence: Christos S. Mantzoros, Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, ST816, Boston, MA 02215, USA. Tel.: +1-617-667-8630; Fax: +1-617-667-8634; E-mail: cmantzor@bidmc.harvard.edu

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Introduction

Statins have a well-documented role in the primary and secondary prevention of cardiovascular disease. Meta-analyses of randomized trials have demonstrated reductions in major coronary events, cardiovascular morbidity and all-cause mortality.[1] Although these effects are mediated mainly by the statin-induced decrease in low-density lipoprotein cholesterol (LDL-C), LDL-C independent effects, such as improvements of insulin resistance (IR), may also account for some of the statin-mediated benefits.[2] Ezetimibe, a potent cholesterol-absorption inhibitor, lowers LDL-C concentrations by approximately 20%. Although cardiovascular end-point studies with ezetimibe in humans are pending, this medication has been shown to inhibit the development of atherosclerosis in ApoE knock-out mice.[3]

Adipokines are hormones secreted by the adipose tissue which have been implicated in the modulation of insulin sensitivity, with adiponectin and leptin having insulin-sensitizing effects and resistin reportedly impairing insulin function.[4] Adipokines have also been implicated in lipid metabolism and in the pathogenesis of atherosclerosis,[5] with adiponectin having anti-atherosclerotic[6] and resistin pro-atherosclerotic effects.[7]

Whether the potential insulin-sensitizing and anti-atherosclerotic effects of statins and/or ezetimibe are mediated through modulation of serum adipokines has not yet been examined. Previous studies examining the effects of statins on adipokines showed no effects on adiponectin levels[8–12] and conflicting results regarding their effects on leptin and resistin.[9,12,13] Finally, no study in humans has until now examined the effects of statins on high molecular weight (HMW) adiponectin or the effect of ezetimibe on any adipokines.

We thus examined the effects of ezetimibe, simvastatin and their combination on serum concentrations of adiponectin, HMW adiponectin, resistin and leptin in healthy adult men. The present

study is, to the best of our knowledge, the first one addressing this question.

Research design and methods

Study design

The study was a one-centre, prospective, randomized, parallel three-group study ($N = 24$ for each group). Subjects were randomized to receive ezetimibe (10 mg/day), simvastatin (40 mg/day) or ezetimibe (10 mg/day) plus simvastatin (40 mg/day) for a period of 2 weeks. Blood was drawn at 8 am in the morning after an overnight fast at days 1 (before the initiation of treatment) and 15 (at the end of the 2-week treatment period).

Subjects

The study protocol was approved by the Ethics Committee of the University of Cologne, and all subjects gave written informed consent. Seventy-two male volunteers were recruited by word of mouth and through advertisements in the Cologne area and on campus. Inclusion criteria were age between 18 and 60 years, body mass index (BMI) between 18·5 and 30 kg/m^2, LDL-C concentrations < 190 mg/dl, triglycerides < 250 mg/dl and normal blood pressure (< 140/90 mmHg). Subjects who had received lipid-lowering drugs within 12 weeks prior to study entry, those with a history of excessive alcohol intake, liver disease, renal dysfunction (glomerular filtration rate < 60 ml/min), coronary heart disease, diabetes or other endocrine disorders, eating disorders, history of recent substantial (> 10%) weight change, history of obesity (BMI > 35 kg/m^2) or taking medications known to affect lipoprotein metabolism were excluded from the study. All patients were advised to keep their usual dietary and exercise habits throughout the trial.

Assays

Total cholesterol, LDL-C and high-density lipoprotein cholesterol (HDL-C) as well as triglycerides were determined in plasma by routine enzymatic methods (CHOD-PAP and GPO-PAP; Roche Diagnostics, Mannheim, Germany). Lipoproteins were analysed on the day of blood collection in the central laboratory of the Cologne University Medical Center. Insulin levels were measured by radioimmunoassay (RIA) (Diagnostic System Laboratories, Inc. Webster, TX; sensitivity, 1·3 μIU/ml; inter- and intra-assay coefficients of variation (CV), 4·7%–12·2% and 4·5%–8·3%, respectively). IR was estimated at baseline using the HOMA index – the product of fasting glucose (mmol/l) and insulin (units/ml) divided by the constant 22·5[14] – the QUICKI, defined as the reciprocal of the sum of the logarithm of fasting insulin and that of fasting glucose: $1/[\log(I) + \log(G)]$[15] as well as the McAuley index ($Mffm/I = \exp[2{\cdot}63 - 0{\cdot}28 \ln(\text{insulin}) - 0{\cdot}31 \ln(\text{triglyceride})]$, where Mffm/l is the insulin sensitivity index corrected for fat-free mass divided by average insulin.[16]

Serum adiponectin, leptin and resistin levels were measured using RIAs (Linco Research, St. Charles, MO, and BioVendor, Brno, Czech Republic), as previously described.[12,17] The sensitivity of the adiponectin assay is 1 ng/ml, intra-assay CV of 6·6%; resistin 0·2 ng/ml, CV 3·4%–5·2%; and leptin 0·5 ng/ml, CV 6%–7%. HMW adiponectin was measured using an ELISA (ALPCO Diagnostics, Salem, NH) as described previously[18] with a sensitivity of 0·04 ng/ml and CV 2·8%–8·4%.

Data analysis

Statistical analyses were performed with StatView 5·0 (SAS Institute, Inc., Cary, NC). Values are expressed as means ± SD. Comparisons between baseline and treatment values were performed using Student's paired *t*-test in case of normally distributed values and using the nonparametric Wilcoxon signed rank test in case of skewed values. Comparisons between groups were performed using analysis of variance and, in case of significant overall *P*-value, also using the *posthoc* tests of Bonferroni and Dunn. Categorical variables were analysed by χ^2 statistics. All analyses were two-sided, and *P*-values of < 0·05 were considered statistically significant. Triglyceride and leptin values were log transformed before statistical analysis. Treatment-induced changes are presented as mean differences and 95% confidence intervals and percent change from baseline.

Results

Mean age of the subjects was 32 ± 9 years (range 20–60 years), mean body weight 85 ± 12 kg (range 64–115 kg) and mean BMI 25·7 ± 3·2 kg/m^2 (range 19·5–32·8 kg/m^2). Forty-two subjects (58%) had never smoked, 9 (13%) were ex-smokers (> 1 year) and 21 (29%) were current smokers. Baseline subject characteristics were not different among the treatment groups (Table 1). All subjects completed the study. All subjects were treated for 14 days. Compliance was excellent based on pill counts (mean compliance 99·1% ± 3·7%). None of the volunteers reported any adverse events including complaints of myalgia or muscle weakness during the study.

BMI

BMI and body weight remained unchanged during the treatment period. There was a positive correlation between leptin at baseline and BMI ($R = 0{\cdot}65$, $P < 0{\cdot}0001$). Baseline adiponectin and HMW adiponectin values correlated negatively with BMI ($R = -0{\cdot}35$, $P = 0{\cdot}0025$ and $R = -0{\cdot}32$, $P = 0{\cdot}0062$, respectively). There was no correlation between baseline resistin and BMI ($R = 0{\cdot}08$, $P = 0{\cdot}52$).

Adipokines

There was a significant inverse relationship between baseline adiponectin and leptin ($R = -0{\cdot}31$, $P = 0{\cdot}007$), and a highly significant correlation between baseline values of adiponectin and HMW adiponectin ($R = 0{\cdot}79$, $P < 0{\cdot}0001$). Leptin correlated positively whereas adiponectin and HMW adiponectin negatively with BMI[19] ($R = 0{\cdot}65$, $P < 0{\cdot}0001$; $R = -0{\cdot}35$, $P = 0{\cdot}0028$; and $R = -0{\cdot}31$, $P = 0{\cdot}0077$, respectively). There was a significant correlation of adiponectin and HMW adiponectin levels with age ($R = 0{\cdot}23$, $P = 0{\cdot}049$ and $R = 0{\cdot}23$, $P = 0{\cdot}047$, respectively), but resistin and leptin did not correlate with age.

Adiponectin, HMW adiponectin and resistin were not correlated with IR as reflected by HOMA index, QUICKI and McAuley index.

Table 1. Baseline characteristics of the randomized subjects. Data are means ± SD

Parameter	All ($n = 72$)	Ezetimibe ($n = 24$)	Simvastatin ($n = 24$)	Ezetimibe plus simvastatin ($n = 24$)	P-value
Age (years)	31·5 ± 9·2	28·6 ± 6·6	31·9 ± 8·8	34·1 ± 11·2	0·11*
Height (cm)	181 ± 7	181 ± 7	182 ± 6	181 ± 7	0·84*
Weight (kg)	85 ± 12	82 ± 11	87 ± 12	84 ± 12	0·28*
Body mass index (kg/m^2)	25·7 ± 3·2	25·0 ± 3·3	26·4 ± 3·2	25·8 ± 3·1	0·35*
Smoker, *n* (%)					
Current smoker	21 (29)	7 (29)	8 (33)	6 (25)	
Ex-smoker	9 (13)	4 (17)	2 (8)	3 (13)	0·90†
Never smoker	42 (58)	13 (54)	14 (58)	15 (63)	
Duration of treatment (days)	14·6 ± 1·8	14·3 ± 0·8	14·8 ± 2·3	14·8 ± 2·0	0·51*
Minimum to maximum duration	14–24	14–18	14–24	14–21	
Adherence (%)‡	99·1 ± 3·7	99·7 ± 1·4	98·5 ± 5·1	99·0 ± 3·6	0·54*
Minimum to maximum adherence	79–100	93–100	79–100	83–100	
Parameters of insulin sensitivity					
HOMA index[14]	1·98 ± 0·96	1·90 ± 1·01	1·88 ± 0·67	2·14 ± 1·12	0·59*
QUICKI[15]	0·35 ± 0·021	0·353 ± 0·023	0·351 ± 0·018	0·347 ± 0·023	0·64*
McAuley index[16]	7·9 ± 1·5	8·4 ± 1·6	7·7 ± 1·3	7·5 ± 1·6	0·09*

*P values were calculated by analysis of variance (ANOVA).
†P values were calculated by two-sided χ^2 test.
‡Adherence was determined by pill count (number of tablets taken divided by number of days treated).

Leptin, however, was positively associated with IR. All aforementioned associations and lack thereof persisted after adjustment for age and BMI.

Lipids

LDL-C decreased by 22% ± 10%, 41% ± 12% and 60% ± 10% and total cholesterol by 11 ± 10, 25 ± 8 and 37 ± 8 in the ezetimibe, simvastatin and combination groups, respectively. All changes were statistically significant (ANOVA $P < 0·0001$). There were no changes in HDL-C concentrations in any of the three treatment groups. There was a positive correlation between leptin at baseline and LDL-C ($R = 0·28$, $P = 0·0017$) which became nonsignificant after adjusting for BMI ($P = 0·48$). There was a borderline negative correlation between adiponectin and LDL-C ($R = -0·21$, $P = 0·07$) and a positive correlation between baseline adiponectin and HDL-C ($R = 0·28$, $P = 0·017$). The correlation of HMW adiponectin and HDL-C was borderline significant ($R = 0·22$, $P = 0·06$) and the negative correlation between baseline HMW adiponectin and LDL-C ($R = -0·25$, $P = 0·0371$) became nonsignificant after adjusting for BMI ($P = 0·48$). There was no correlation between baseline resistin and LDL-C ($R = -0·10$, $P = 0·38$) or any other lipid parameter.

There was a negative correlation between leptin at baseline and HDL-C ($R = –0·36$, $P = 0·0017$) which remained significant after adjusting for BMI. There was no correlation between baseline adipokines and triglycerides.

Effects of treatment on adipokines

There was no effect of treatment with ezetimibe and/or simvastatin on adiponectin, HMW adiponectin, resistin and leptin concentrations (Table 2), and/or percent change of adiponectin, HMW adiponectin, leptin or resistin.

Discussion

Lipid-lowering therapy has significantly contributed to the reduction of cardiovascular morbidity and mortality either through LDL lowering or through improvements of IR and metabolic profile, which is postulated to be affected by adipokines.[20,21] We have thus investigated the effects of two lipid-lowering medications, simvastatin and ezetimibe, alone and in combination, on serum adipokine levels in healthy men.

There is substantial evidence for the existence of a cross-talk between statins and peroxisome proliferator-activated receptor (PPAR) pathways,[22–25] and a functional PPAR-responsive element (PPRE) has been identified in the human adiponectin promoter.[26] Therefore, statins could possibly modulate plasma adiponectin levels through PPAR modulation. Furthermore, ezetimibe has been shown to modulate sterol regulatory element binding protein (SREBP) expression.[27,28] Therefore, ezetimibe could also possibly modulate plasma adiponectin levels through SREBP modulation, as SREBP has been shown to regulate adiponectin gene expression.[29]

Adipokines, hormones secreted by the adipose tissue, have been implicated in the pathogenesis of IR, the metabolic syndrome and atherosclerosis.[4,5] Adiponectin and its biologically active form HMW adiponectin, in addition to improving IR and metabolic and lipid profiles, have been shown to have atheroprotective effects by stimulating the production of nitric oxide, reducing the expression of adhesion molecules in endothelial cells, decreasing the cytokine production from macrophages, improving endothelium-dependent vasodilatation, suppressing macrophage-to-foam cell transformation,

Table 2. Effects of treatment on adipokine concentrations. Data are means ± SD

Parameter	Treatment ($N = 24$ in each group)	Baseline	2 weeks	Mean difference (95% CI)	Percent change from baseline	*P*-value*
Adiponectin (μg/ml)	Ezetimibe	13·17 ± 5·97	12·95 ± 5·96	–0·23 (–1·09 to +0·63)	–0·03 ± 26·3	0·48
	Simvastatin	13·28 ± 5·29	14·03 ± 5·49	+0·74 (–0·40 to +1·88)	+9·29 ± 26·1	0·17
	Ezetimibe + simvastatin	13·63 ± 4·88	14·36 ± 5·08	+0·73 (–0·52 to +2·0)	+8·94 ± 27·4	0·22
High molecular weight adiponectin (μg/ml)	Ezetimibe	2·80 ± 2·29	2·77 ± 2·14	–0·03 (–0·35 to +0·28)	+2·28 ± 21·9	0·83
	Simvastatin	2·79 ± 2·06	3·04 ± 2·40	+0·24 (–0·15 to +0·63)	+11·1 ± 32·5	0·22
	Ezetimibe + simvastatin	2·52 ± 1·61	2·72 ± 1·41	+0·20 (–0·15 to +0·55)	+15·3 ± 31·3	0·24
Leptin (μg/ml)	Ezetimibe	2·63 ± 2·94	2·80 ± 3·93	+0·17 (–0·62 to +0·96)	+6·40 ± 35·4	0·75
	Simvastatin	3·40 ± 2·97	3·69 ± 3·25	+0·30 (–0·41 to +1·01)	+10·2 ± 40·2	0·71
	Ezetimibe + simvastatin	2·85 ± 2·47	3·32 ± 3·44	+0·47 (–0·30 to +1·25)	+13·9 ± 53·7	0·63
Resistin (ng/ml)	Ezetimibe	14·39 ± 5·29	13·62 ± 4·03	–0·77 (–2·56 to +1·02)	–0·75 ± 23·0	0·80
	Simvastatin	13·78 ± 6·42	13·06 ± 3·30	–0·72 (–2·51 to +1.07)	+2·66 ± 22·3	0·999
	Ezetimibe + simvastatin	14·08 ± 4·19	14·06 ± 5·26	–0·02 (–1·47 to +1·44)	+0·70 ± 21·9	0·86

*Wilcoxon signed rank test.

inhibiting the expression of scavenger receptor class A-1 of macrophages and suppressing the proliferation and migration of smooth muscle cells.[6] Furthermore, low adiponectin levels correlate significantly and independently with the development of coronary artery disease and are associated with progression of coronary artery calcification independently of other cardiovascular risk factors.[6] Leptin exerts *in vitro* potential pro-atherogenic effects such as induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation, migration, and hypertrophy and proliferation of vascular smooth muscle cells.[30] Large prospective cohort studies have shown associations between leptin and lipid levels but have failed to show an independent association between circulating leptin levels and cardiovascular morbidity or mortality.[31] Finally, resistin has been found to have pro-inflammatory effects, to up-regulate adhesion molecules and to induce human aortic smooth muscle proliferation;[7] but the association of resistin with IR, metabolic and lipid profile remains controversial.[32,33] Reilly *et al.*[34] have recently shown a pro-atherosclerotic effect of resistin and found resistin to be associated with increased coronary artery calcification.

Previous studies examining the effects of statins on adipokines showed no effects on adiponectin levels[8–12] and conflicting results regarding their effects on leptin and resistin.[9,12,13] We found that a 12-week atorvastatin treatment does not affect adiponectin levels.[12] We examined for the first time herein the effects of simvastatin on circulating levels of not only total but also HMW adiponectin, and we report no significant effect of simvastatin on circulating total and HMW adiponectin in healthy subjects. These results are in agreement with previous reports showing no effect of various statins, including simvastatin, atorvastatin and pravastatin, on adiponectin levels.[8,9] In contrast, a recent study by Forst *et al*. found that simvastatin decreases adiponectin in diabetic subjects.[14]

The effects of statins on leptin levels have been contradictory to date. Atorvastatin has been found to reduce leptin in patients with type 2 diabetes,[13] while pravastatin had no effect on leptin levels in healthy adults.[9] Similarly, we report no effect of simvastatin therapy on leptin levels. Whether a specific statin effect (simvastatin *vs.* atorvastatin *vs.* pravastatin) exists, remains to be studied in the future. We also observed no effects of simvastatin on serum resistin levels in accordance to our previous findings[12] and to a recent report from Chu *et al.*[8] In contrast, von Eynatten *et al*. found a statin-induced decrease in resistin levels in patients with type 2 diabetes.[13]

Our study is also the first one to examine the effects of ezetimibe on circulating adipokines. We show that ezetimibe does not affect serum adipokine levels, either alone or in combination with simvastatin. These data in healthy humans are consistent with a study in hyperinsulinaemic hamsters where ezetimibe had no effect on serum leptin levels[33] while other adipokines were not measured in that study.

We also examined the associations of various adipokines with anthropometric parameters, plasma lipoprotein concentrations and parameters of IR, as these associations have not been adequately studied in non-obese subjects. The validity of this study is supported by the fact that we confirm expected associations between adipokines and anthropometric and metabolic parameters. In agreement to previous reports, leptin was positively and adiponectin and HMW adiponectin negatively correlated with BMI,[9] while there was no association between resistin and BMI.[32] There was a positive correlation between adiponectin, but no correlation of resistin or leptin, and age as previously described.[32,35,36] Additionally, we found an inverse association between leptin and adiponectin, as previously described.[37] Adiponectin was positively and leptin negatively associated with HDL-C in accordance to recent reports.[17,37] The present study also shows a negative relationship between plasma adiponectin and LDL-C in healthy adults. Okada *et al.*[38] have reported a similar relationship in 11- to 12-year-old girls and Bansal *et al.*[39] in umbilical cord blood. We found that leptin was positively associated with LDL-C concentrations in agreement to previous findings.[40]

Additionally, we were able to confirm that leptin levels are correlated with IR as recently described.[41] Resistin levels were not associated with IR, in agreement with previous findings.[42] The lack of an association between IR and adiponectin, as previously shown,[43,44] may appear to be surprising, but previous studies have also reported no association between adiponectin and IR[43,44] in normal-weight individuals.[45] As plasma adiponectin has been recently shown to be

correlated with IR in obese but not in lean subjects,[19] adiponectin may not be a major determinant of IR in healthy, non-obese subjects, with a narrow range of apparently normal adiponectin levels.

Strengths of our study are its randomized design, the high adherence of the subjects to treatment (determined by pill count) and the lack of any concomitant treatment that could affect the results. Although the lack of a placebo-treated control group could be considered a limitation of the study, it could be claimed that no changes in a placebo arm would have been expected as body weight, BMI, diet and exercise did not change during the study. This is further supported by the lack of significant changes in the circulating adipokine levels in the actively treated groups. A 2-week-long treatment period may have been too short to detect significant changes of adipokine levels in healthy men for whom only little room for improvement might have been left. Thus, further larger studies with longer treatment periods in both healthy and obese subjects with the metabolic syndrome will be needed to confirm our findings.

In summary, the findings of this study show that ezetimibe and simvastatin, alone and in combination, do not affect serum adiponectin, high molecular weight adiponectin, resistin and leptin levels. Thus, metabolically beneficial effects of these medications may be independent from any changes in serum adipokines.

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References

1 LaRosa, J.C., He, J. & Vupputuri, S. (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association*, **282**, 2340–2346.

2 Liao, J.K. (2005) Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. *American Journal of Cardiology*, **96**, 24F–33F.

3 Davis, H.R. Jr, Compton, D.S., Hoos, L. & Tetzloff, G. (2001) Ezetimibe, a potent cholesterol absorption inhibitor, inhibits the development of atherosclerosis in ApoE knockout mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **21**, 2032–2038.

4 Sethi, J.K. & Vidal-Puig, A.J. (2007) Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. *Journal of Lipid Research*, **48**, 1253–1262.

5 Han, S.H., Quon, M.J., Kim, J.A. & Koh, K.K. (2007) Adiponectin and cardiovascular disease: response to therapeutic interventions. *Journal of the American College of Cardiology*, **49**, 531–538.

6 Kadowaki, T. & Yamauchi, T. (2005) Adiponectin and adiponectin receptors. *Endocrine Reviews*, **26**, 439–451.

7 McTernan, P.G., Kusminski, C.M. & Kumar, S. (2006) Resistin. *Current Opinions in Lipidology*, **17**, 170–175.

8 Chu, C.S., Lee, K.T., Lee, M.Y., Su, H.M., Voon, W.C., Sheu, S.H. & Lai, W.T. (2006) Effects of atorvastatin and atorvastatin withdrawal on soluble CD40L and adipocytokines in patients with hypercholesterolaemia. *Acta Cardiologica*, **61**, 263–269.

9 Gannage-Yared, M.H., Azar, R.R., mm-Azar, M., Khalife, S., Germanos-Haddad, M., Neemtallah, R. & Halaby, G. (2005) Pravastatin does not affect insulin sensitivity and adipocytokines levels in healthy nondiabetic patients. *Metabolism*, **54**, 947–951.

10 Koh, K.K., Quon, M.J., Han, S.H., Chung, W.J., Ahn, J.Y., Seo, Y.H., Choi, I.S. & Shin, E.K. (2005) Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. *Journal of the American College of Cardiology*, **45**, 1649–1653.

11 Koh, K.K., Quon, M.J., Han, S.H., Ahn, J.Y., Jin, D.K., Kim, H.S., Kim, D.S. & Shin, E.K. (2005) Vascular and metabolic effects of combined therapy with ramipril and simvastatin in patients with type 2 diabetes. *Hypertension*, **45**, 1088–1093.

12 Shetty, G.K., Economides, P.A., Horton, E.S., Mantzoros, C.S. & Veves, A. (2004) Circulating adiponectin and resistin levels in relation to metabolic factors, inflammatory markers, and vascular reactivity in diabetic patients and subjects at risk for diabetes. *Diabetes Care*, **27**, 2450–2457.

13 von, E.M., Schneider, J.G., Hadziselimovic, S., Hamann, A., Bierhaus, A., Nawroth, P.P. & Dugi, K.A. (2005) Adipocytokines as a novel target for the anti-inflammatory effect of atorvastatin in patients with type 2 diabetes. *Diabetes Care*, **28**, 754–755.

14 Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F. & Turner, R.C. (1985) Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, **28**, 412–419.

15 Katz, A., Nambi, S.S., Mather, K., Baron, A.D., Follmann, D.A., Sullivan, G. & Quon, M.J. (2000) Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *Journal of Clinical Endocrinology and Metabolism*, **85**, 2402–2410.

16 McAuley, K.A., Williams, S.M., Mann, J.I., Walker, R.J., Lewis-Barned, N.J., Temple, L.A. & Duncan, A.W. (2001) Diagnosing insulin resistance in the general population. *Diabetes Care*, **24**, 460–464.

17 Mantzoros, C.S., Li, T., Manson, J.E., Meigs, J.B. & Hu, F.B. (2005) Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism*, **90**, 4542–4548.

18 Bluher, M., Brennan, A.M., Kelesidis, T., Kratzsch, J., Fasshauer, M., Kralisch, S., Williams, C.J. & Mantzoros, C.S. (2007) Total and high-molecular weight adiponectin in relation to metabolic variables at baseline and in response to an exercise treatment program: comparative evaluation of three assays. *Diabetes Care*, **30**, 280–285.

19 Kantartzis, K., Fritsche, A., Tschritter, O., Thamer, C., Haap, M., Schafer, S., Stumvoll, M., Haring, H.U. & Stefan, N. (2005) The association between plasma adiponectin and insulin sensitivity in humans depends on obesity. *Obesity Research*, **13**, 1683–1691.

20 Westphal, S., Borucki, K., Taneva, E., Makarova, R. & Luley, C. (2006) Adipokines and treatment with niacin. *Metabolism*, **55**, 1283–1285.

21 Yin, W.H., Jen, H.L., Chen, J.W., Lin, S.J. & Young, M.S. (2006) Differential effects of peroxisome proliferator-activated receptor

ligands and sulfonylurea plus statin treatment on plasma concentrations of adipokines in type 2 diabetes with dyslipidemia. *Diabetes Metabolism*, **32**, 229–235.

22 Fajas, L., Schoonjans, K., Gelman, L., Kim, J.B., Najib, J., Martin, G., Fruchart, J.C., Briggs, M., Spiegelman, B.M. & Auwerx, J. (1999) Regulation of peroxisome proliferator-activated receptor γ expression by adipocyte differentiation and determination factor 1/sterol regulatory element binding protein 1: implications for adipocyte differentiation and metabolism. *Molecular Cell Biology*, **19**, 5495–5503.

23 Landrier, J.F., Thomas, C., Grober, J., Duez, H., Percevault, F., Souidi, M., Linard, C., Staels, B. & Besnard, P. (2004) Statin induction of liver fatty acid-binding protein (L-FABP) gene expression is peroxisome proliferator-activated receptor-α-dependent. *Journal of Biological Chemistry*, **279**, 45512–45518.

24 Martin, G., Duez, H., Blanquart, C., Berezowski, V., Poulain, P., Fruchart, J.C., Najib-Fruchart, J., Glineur, C. & Staels, B. (2001) Statin-induced inhibition of the Rho-signaling pathway activates PPARα and induces HDL apoA-I. *Journal of Clinical Investigations*, **107**, 1423–1432.

25 Yano, M., Matsumura, T., Senokuchi, T., Ishii, N., Murata, Y., Taketa, K., Motoshima, H., Taguchi, T., Sonoda, K., Kukidome, D., Takuwa, Y., Kawada, T., Brownlee, M., Nishikawa, T. & Araki, E. (2007) Statins activate peroxisome proliferator-activated receptor γ through extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent cyclooxygenase-2 expression in macrophages. *Circulation Research*, **100**, 1442–1451.

26 Iwaki, M., Matsuda, M., Maeda, N., Funahashi, T., Matsuzawa, Y., Makishima, M. & Shimomura, I. (2003) Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes*, **52**, 1655–1663.

27 During, A., Dawson, H.D. & Harrison, E.H. (2005) Carotenoid transport is decreased and expression of the lipid transporters SR-BI, NPC1L1, and ABCA1 is downregulated in Caco-2 cells treated with ezetimibe. *Journal of Nutrition*, **135**, 2305–2312.

28 Telford, D.E., Sutherland, B.G., Edwards, J.Y., Andrews, J.D., Barrett, P.H. & Huff, M.W. (2007) The molecular mechanisms underlying the reduction of LDL apoB-100 by ezetimibe plus simvastatin. *Journal of Lipid Research*, **48**, 699–708.

29 Seo, J.B., Moon, H.M., Noh, M.J., Lee, Y.S., Jeong, H.W., Yoo, E.J., Kim, W.S., Park, J., Youn, B.S., Kim, J.W., Park, S.D. & Kim, J.B. (2004) Adipocyte determination- and differentiation-dependent factor 1/sterol regulatory element-binding protein 1c regulates mouse adiponectin expression. *Journal of Biological Chemistry*, **279**, 22108–22117.

30 Brennan, A.M. & Mantzoros, C.S. (2006) Drug insight: the role of leptin in human physiology and pathophysiology – emerging clinical applications. *Nature Clinical Practice Endocrinological Metabolism*, **2**, 318–327.

31 Brennan, A.M., Li, T.Y., Kelesidis, I., Gavrila, A., Hu, F.B. & Mantzoros, C.S. (2007) Circulating leptin levels are not associated with cardiovascular morbidity and mortality in women with diabetes: a prospective cohort study. *Diabetologia*, **50**, 1178–1185.

32 Pantsulaia, I., Livshits, G., Trofimov, S. & Kobyliansky, E. (2007) Genetic and environmental determinants of circulating resistin level in a community-based sample. *European Journal of Endocrinology*, **156**, 129–135.

33 van, H.M., Austin, T.M., Farley, C., Cook, J.A., Tetzloff, G.G. & Davis, H.R. (2001) Ezetimibe, a potent cholesterol absorption inhibitor, normalizes combined dyslipidemia in obese hyperinsulinemic hamsters. *Diabetes*, **50**, 1330–1335.

34 Reilly, M.P., Lehrke, M., Wolfe, M.L., Rohatgi, A., Lazar, M.A. & Rader, D.J. (2005) Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation*, **111**, 932–939.

35 Jurimae, J. & Jurimae, T. (2007) Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables. *American Journal of Physiological and Endocrinological Metabolism*, **293**, E42–E47.

36 Magni, P., Liuzzi, A., Ruscica, M., Dozio, E., Ferrario, S., Bussi, I., Minocci, A., Castagna, A., Motta, M. & Savia, G. (2005) Free and bound plasma leptin in normal weight and obese men and women: relationship with body composition, resting energy expenditure, insulin-sensitivity, lipid profile and macronutrient preference. *Clinical Endocrinology*, **62**, 189–196.

37 Snijder, M.B., Heine, R.J., Seidell, J.C., Bouter, L.M., Stehouwer, C.D., Nijpels, G., Funahashi, T., Matsuzawa, Y., Shimomura, I. & Dekker, J.M. (2006) Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the Hoorn study. *Diabetes Care*, **29**, 2498–2503.

38 Okada, T., Saito, E., Kuromori, Y., Miyashita, M., Iwata, F., Hara, M. & Harada, K. (2006) Relationship between serum adiponectin level and lipid composition in each lipoprotein fraction in adolescent children. *Atherosclerosis*, **188**, 179–183.

39 Bansal, N., Charlton-Menys, V., Pemberton, P., McElduff, P., Oldroyd, J., Vyas, A., Koudsi, A., Clayton, P.E., Cruickshank, J.K. & Durrington, P.N. (2006) Adiponectin in umbilical cord blood is inversely related to low-density lipoprotein cholesterol but not ethnicity. *Journal of Clinical Endocrinology and Metabolism*, **91**, 2244–2249.

40 Hirose, H., Saito, I., Kawai, T., Tsujioka, M., Kawabe, H. & Saruta, T. (2001) Relationships between baseline serum leptin levels and 2-year changes in body mass index, blood pressure and metabolic parameters in Japanese male adolescents and middle-aged men. *Clinical Science*, **100**, 145–150.

41 Wannamethee, S.G., Tchernova, J., Whincup, P., Lowe, G.D., Kelly, A., Rumley, A., Wallace, A.M. & Sattar, N. (2007) Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease. *Atherosclerosis*, **191**, 418–426.

42 Heilbronn, L.K., Rood, J., Janderova, L., Albu, J.B., Kelley, D.E., Ravussin, E. & Smith, S.R. (2004) Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. *Journal of Clinical Endocrinology and Metabolism*, **89**, 1844–1848.

43 Gavrila, A., Chan, J.L., Yiannakouris, N., Kontogianni, M., Miller, L.C., Orlova, C. & Mantzoros, C.S. (2003) Serum adiponectin levels are inversely associated with overall and central fat distribution but are not directly regulated by acute fasting or leptin administration in humans: cross-sectional and interventional studies. *Journal of Clinical Endocrinology and Metabolism*, **88**, 4823–4831.

44 Silha, J.V., Krsek, M., Skrha, J.V., Sucharda, P., Nyomba, B.L. & Murphy, L.J. (2003) Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. *European Journal of Endocrinology*, **149**, 331–335.

45 Heliovaara, M.K., Strandberg, T.E., Karonen, S.L. & Ebeling, P. (2006) Association of serum adiponectin concentration to lipid and glucose metabolism in healthy humans. *Hormone Metabolism Research*, **38**, 336–340.

