Effect of Atorvastatin and Fish Oil on Plasma High-Sensitivity C-Reactive Protein Concentrations in Individuals with Visceral Obesity

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Background: Chronic low-grade inflammation may contribute to the increased risk of atherosclerosis in visceral obesity. Statin and fish oil have been reported to have antiinflammatory effects. We studied whether dyslipidemic, obese individuals have increased plasma high-sensitivity C-reactive protein (hs-CRP) concentrations and whether treatment with atorvastatin and fish oil lowered plasma hs-CRP concentrations.

Methods: We compared plasma hs-CRP, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) concentrations in 48 obese individuals with the concentrations in 10 lean normolipidemic men. The obese individuals were then randomized to treatment with atorvastatin (40 mg/day), fish oil (4 g/day), atorvastatin plus fish oil, or matching placebo for 6 weeks.

Results: Compared with controls, obese individuals had increased hs-CRP [geometric mean, 2.19 mg/L (95% confidence interval, 2.15–3.15 mg/L) vs 0.49 mg/L (0.30–0.93 mg/L); P <0.001] and IL-6 [351 pg/L (318–449 pg/L) vs 251 pg/L (211–305 pg/L); P <0.01]. Atorvastatin treatment had a significant main effect of decreasing plasma hs-CRP (−0.87 mg/L; 95% confidence interval, −0.10 to −1.60 mg/L; P <0.01) and IL-6 (−70 pg/L; 10 to −140 pg/L; P <0.01), but this was not seen with fish oil. The reductions in hs-CRP with atorvastatin were not significantly correlated to changes in plasma lipids, IL-6, insulin resistance, or cholesterogenesis. Plasma TNF-α concentrations in obese individuals, however, were neither statistically different from concentrations in the lean controls nor altered with atorvastatin or fish oil treatment.

Conclusions: This study shows that visceral obesity is associated with increased plasma hs-CRP and IL-6 and, hence, a low-grade chronic inflammatory state and that treatment with atorvastatin or atorvastatin with fish oil, but not fish oil alone, reverses this abnormality.

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Atherosclerosis has been recognized as a chronic inflammatory process (*1*). Prospective studies have shown that increased plasma concentrations of high-sensitivity C-reactive protein (hs-CRP),[1] a sensitive marker for low-grade inflammation, are associated with increased risk of cardiovascular events (*2*). Obesity is a major risk factor for cardiovascular disease (CVD). The precise reason for the increased risk of CVD in obesity remains unclear, but it may be attributable to insulin resistance and dyslipidemia (*3*). Increasing evidence suggests that increased hs-CRP concentrations are also associated with obesity and a cluster of altered metabolic risk factors related to visceral obesity, such as hyperinsulinemia, hypertriglyceridemia, and low HDL (*4–8*). Increased hs-CRP may therefore be a risk factor contributing to the increased risk of CVD in visceral obesity, and this remains to be elucidated.

Hydroxymethylglutaryl-CoA reductase inhibitors (statins) and fish oil are well-known lipid-regulating agents (*9, 10*). Statins lower plasma cholesterol, LDL-cholesterol (LDL-C), and apolipoprotein B (apoB) by inhibiting cholesterol synthesis and up-regulating hepatic receptor-mediated clearance of apoB-containing lipopro-

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[1] Nonstandard abbreviations: hs-CRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; LDL-C and HDL-C, LDL- and HDL-cholesterol, respectively; apo, apolipoprotein; BMI, body mass index; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; IL, interleukin; TNF-α, tumor necrosis factor-α; NEFA, nonesterified fatty acid; HOMA, homeostasis model assessment; and CI, confidence interval.

teins (9). Fish oil lowers endogenous hypertriglyceridemia by inhibiting triglyceride synthesis and triglyceride-rich VLDL-apoB secretion (10). Clinical trials with statins or fish oil have demonstrated a significant reduction in cardiovascular events (11–14). These may be related not only to the beneficial effects on plasma lipids, but also to other non-lipid-lowering benefits of these agents, including antiinflammatory effects (15–17).

The effects of statins and fish oil on inflammatory markers and, in particular, plasma hs-CRP have not yet been examined in obesity. We therefore studied whether dyslipidemic viscerally obese individuals have increased plasma hs-CRP concentrations and whether randomized treatments with atorvastatin and fish oil reduce hs-CRP concentrations.

Materials and Methods

PATIENTS

We recruited 48 obese men [body mass index (BMI) >29 kg/m², waist circumference >100 cm; waist-to-hip ratio >0.97] with dyslipidemia at screening (total cholesterol >5.2 mmol/L and triglycerides >1.2 mmol/L) and 10 normolipidemic lean men of similar age for the study. None of the participants had diabetes mellitus (excluded by oral glucose tolerance test), macroproteinuria, creatinemia (>120μmol/L), hypothyroidism, abnormal liver and muscle enzymes, or consumed >30 g of alcohol/day. None reported a history of CVD or familial hyperlipidemia or were taking medication or other agents known to affect lipid metabolism or inflammatory response. The study was approved by the Royal Perth Hospital Ethics Committee, and all participants gave informed written consent.

CROSS-SECTIONAL STUDY AND INTERVENTION

At baseline, venous blood was collected from all participants after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements. Obese individuals then entered a randomized, double-blind, placebo-controlled intervention trial involving a 3-week run-in period during which they were required to continue habitual diets and to demonstrate that body weight did not vary by more than 2%. At the end of this period they were randomized to one of the four treatment groups for 6 weeks: 40 mg/day atorvastatin (placebo, 4 g/day corn coil); Omacor™ capsules, 4 g/day [45% eicosapentaenoic acid (EPA) and 39% docosahexaenoic acid (DHA) as ethyl esters; plus atorvastatin placebo]; 40 mg/day atorvastatin plus 4 g/day Omacor; or atorvastatin placebo plus 4 g/day corn oil (placebo group). All were advised to continue their habitual isocaloric diet and to keep physical exercise constant. Compliance with the atorvastatin and fish oil regimen was checked by tablet count at weeks 3 and 6. Evidence of adherence to the fish oil capsules in the fish and atorvastatin-plus-fish oil groups was also obtained from measurement of plasma EPA and DHA concentrations. Clinical and nutritional details were re-

corded at the start and end of the study. Dietary intake was assessed for energy and major nutrients, using at least two 24-h dietary diaries at the beginning and end of the study. Diets were subsequently analyzed using DIET 4 Nutrient Calculation Software (Xyris Software).

BIOCHEMICAL METHODS

Plasma triglyceride and cholesterol concentrations were determined by standard enzymatic methods on a Hitachi 917 Biochemical Analyzer. HDL-C was measured by a homogeneous, enzymatic colorimetric method using a commercial reagent set (Roche Diagnostics). LDL-C was calculated using the Friedewald equation. Non-HDL-C was derived as total cholesterol minus HDL-C. Plasma apoB and apoA-I were determined by immunonephelometry. Plasma hs-CRP was measured using a high-sensitivity monoclonal antibody assay (Dade Behring Marburg GmbH), as described previously (18). According to the manufacturer's instructions, the lowest detection limit is <0.0175 mg/L. Plasma interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured by immunoassay (R&D Systems). Plasma nonesterified fatty acids (NEFAs) were measured by an enzymatic, colorimetric method using a commercial reagent set (Randox). Plasma insulin was measured by RIA (DiaSorini s.r.l.). Plasma glucose concentrations were measured by an hexokinase

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Table 1. Clinical and biochemical characteristics of participants at baseline.[a]

	Lean (n = 10)	Obese (n = 48)
Age, years	53.1 ± 9.0	53.5 ± 9.0
Body weight, kg	78 ± 12.0	104 ± 15[b]
BMI, kg/m²	24.8 ± 2.9	33.6 ± 4.1[b]
Waist, cm	91.0 ± 9.0	113 ± 9[b]
Waist-to-hip ratio	0.92 ± 0.06	1.01 ± 0.05[b]
Systolic blood pressure, mmHg	122 ± 12	133 ± 15
Diastolic blood pressure, mmHg	71.9 ± 8.3	78.5 ± 10.1
Fasting NEFAs, mmol/L	0.28 ± 0.10	0.29 ± 0.13
Fasting glucose, mmol/L	5.35 ± 0.25	5.46 ± 0.72
Fasting insulin, mIU/L	23.9 ± 4.2	33.8 ± 11.4[b]
Insulin resistance, HOMA score	5.70 ± 1.20	8.36 ± 3.68[b]
Total cholesterol, mmol/L	4.33 ± 0.34	5.95 ± 0.75[b]
Total triglycerides, mmol/L	0.77 ± 0.25	1.90 ± 0.77[b]
HDL-C, mmol/L	1.28 ± 0.30	1.04 ± 0.21[c]
LDL-C, mmol/L	2.70 ± 0.33	3.89 ± 0.68[b]
apoA-I, mg/L	1310 ± 210	1240 ± 180
apoB-100, mg/L	780 ± 110	1280 ± 190[b]
hs-CRP, mg/L	0.49 (0.30–0.93)	2.19 (2.15–3.15)[b]
IL-6, pg/L	251 (211–305)	351 (318–449)[d]
TNF-α, pg/L	453 (367–576)	446 (424–488)

[a] Data are presented as mean ± SD unless otherwise indicated. hs-CRP, IL-6, and TNF-α are given as geometric mean (95% CI).

[b–d] Compared with lean controls by unpaired t-test: [b] $P <0.001$; [c] $P <0.05$; [d] $P <0.01$.

method on the Hitachi 917. Insulin resistance was estimated by homeostasis model assessment (HOMA) as described by Matthews et al. [19]. The plasma lathosterol concentration was assayed by a modification of the method of Mori et al. [20]. Plasma EPA and DHA concentrations were measured using gas chromatography with a Model 5980A gas chromatograph equipped with a 3393A computing integrator (Hewlett-Packard) as described by Mori et al. [21]. Plasma liver (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) and muscle (creatinine kinase) enzymes were measured at the beginning and end of the study. The interassay CVs for all measurements were <5%.

STATISTICAL ANALYSIS

All analyses were carried out using SPSS 10.1 (SPSS Software). Because the distributions of hs-CRP, IL-6, and TNF-α were skewed, they were natural-log-transformed for all analyses. Two-group comparisons (obese vs lean individuals) were performed with independent t-tests. Within-group comparisons were performed with paired t-tests. Differences between the four obese groups were determined by one-way ANOVA. General linear modeling with adjustment for differences in baseline covariates was used to assess the main and interactive effects of atorvastatin and fish oil. Associations between hs-CRP and clinical and biochemical variables were assessed by linear regression of log hs-CRP on each variable separately. Statistical significance was defined as P <0.05.

Results

The clinical and biochemical characteristics of the obese and lean men are shown in Table 1. Age and blood pressures were not significantly different between the groups. The obese group had a significantly higher body weight, BMI, waist circumference, and waist-to-hip ratio compared with the lean group (P <0.001). Although plasma glucose and NEFAs were not significantly different between groups, plasma insulin concentrations and HOMA scores were significantly higher in the obese group (P <0.001). The obese group had significantly higher plasma cholesterol, triglycerides, LDL-C, and apoB (P <0.001), but lower HDL-C (P <0.05) compared with the lean men. Mean daily energy intake was significantly higher in the obese than in controls (9904 ± 197 vs 7316 ± 682 kJ; P = 0.004). The proportion of energy intake from carbohydrates, protein, fat, and alcohol did not differ between the two groups.

Plasma hs-CRP was 4.5-fold higher in the obese group than in the lean group: geometric mean, 2.19 mg/L [95% confidence interval (CI), 2.15–3.15 mg/L] vs 0.49 mg/L (0.30–0.93 mg/L); P <0.001. Plasma IL-6 was also higher in the obese group than in the lean group: 351 pg/L (95% CI, 318–449 pg/L) vs 251 pg/L (211–305 pg/L); P <0.01. However, there was no statistically significant difference in plasma TNF-α concentrations between the two groups. In the obese group, plasma hs-CRP was significantly and

Table 2. Fasting plasma lipids, lipoproteins, lathosterol, HOMA score, hs-CRP, IL-6, and TNF-α at baseline and postintervention in the four groups.[a]

	Placebo (n = 12)		Atorvastatin (n = 13)		Fish oil (n = 12)		Atorvastatin + fish oil (n = 11)		Main effects,[b] P	
	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6	Atorvastatin	Fish oil
Triglycerides, mmol/L	1.7 ± 0.18	1.6 ± 0.15	1.9 ± 0.13	1.4 ± 0.12[c]	2.0 ± 0.34	1.5 ± 0.21[d]	2.0 ± 0.21	1.2 ± 0.17[c]	0.002	0.002
Cholesterol, mmol/L	5.8 ± 0.14	5.6 ± 0.13	5.8 ± 0.17	3.6 ± 0.12[c]	5.9 ± 0.22	5.5 ± 0.22	6.3 ± 0.32	3.9 ± 0.27[c]	0.001	NS[f]
HDL-C, mmol/L	1.05 ± 0.06	1.03 ± 0.06	1.00 ± 0.05	1.04 ± 0.05	0.99 ± 0.06	1.00 ± 0.04	1.10 ± 0.09	1.25 ± 0.09[e]	0.007	0.041
LDL-C, mmol/L	3.8 ± 0.13	3.83 ± 0.11	3.8 ± 0.16	1.8 ± 0.12[c]	3.9 ± 0.22	3.7 ± 0.17	4.0 ± 0.28	2.2 ± 0.19[c]	0.001	NS
apoA-I, mg/L	1280 ± 50	1260 ± 40	1190 ± 50	1230 ± 40	1180 ± 40	1210 ± 40	1280 ± 60	1350 ± 90	NS	NS
apoB, mg/L	1290 ± 40	1230 ± 30	1220 ± 60	690 ± 30[c]	1280 ± 60	1180 ± 60	1340 ± 60	730 ± 50[c]	0.001	NS
Lathosterol, μmol/L	9.3 ± 1.0	9.6 ± 0.7	10.8 ± 1.2	1.9 ± 0.3[c]	11.2 ± 1.5	11.2 ± 1.1	13.0 ± 1.0	3.8 ± 1.1[c]	0.001	NS
HOMA score	7.7 ± 0.7	7.4 ± 0.6	8.1 ± 1.0	8.0 ± 1.2	10.4 ± 1.4	12.1 ± 2.4	7.1 ± 0.9	7.6 ± 0.7	NS	NS
hs-CRP, mg/L	2.04 (1.6–3.1)	1.97 (1.1–4.0)	2.60 (1.9–4.2)	1.80[d] (1.3–3.2)	2.11 (1.6–3.2)	2.09 (1.6–3.0)	2.20 (1.2–4.4)	1.14[e] (0.6–2.4)	0.004	NS
IL-6, pg/L	303 (243–384)	324 (245–442)	363 (298–462)	301[e] (256–368)	331 (254–452)	351 (277–468)	416 (219–773)	309[e] (214–452)	0.005	NS
TNF-α, pg/L	426 (346–533)	443 (359–554)	439 (377–522)	446 (386–526)	463 (409–529)	516 (344–785)	455 (289–536)	434 (370–519)	NS	NS

[a] Data are presented as the mean ± SE unless otherwise indicated. hs-CRP, IL-6, and TNF-α are presented as geometric means (95% CI).

[b] General linear modeling was used to assess the main and interactive effects of atorvastatin and fish oil treatments. There were no significant interactive effects between the treatments.

[c–e] Comparison between pre- and posttreatment data within the group by paired t-test: [c] P <0.001; [d] P <0.05; [e] P <0.01.

[f] NS, not significant.

positively associated with BMI ($r = 0.342$; $P <0.05$), IL-6 ($r = 0.324$; $P <0.05$), and insulin ($r = 0.342$; $P <0.05$) and inversely correlated with HDL-C ($r = -0.325$; $P <0.05$).

Capsule counts confirmed that compliance with randomization to active intervention or placebo was >95%. Plasma EPA and DHA concentrations also increased, from 1.0% ± 0.4% to 3.5% ± 1.3% and from 1.6% ± 0.5% to 3.1% ± 0.8% (both $P <0.001$), respectively, confirming therapeutic compliance with fish oil capsules in the two groups concerned. No participants reported untoward clinical side effects or showed significant increases in liver or muscle enzymes. Body weight, waist circumference, waist-to-hip ratio, BMI, blood pressures, plasma glucose, and insulin did not alter significantly before and after treatments (data not shown). Dietary intake of carbohydrate, fat, protein, alcohol, and total energy did not alter significantly in either of the treatment groups during the study.

The plasma lipid, lipoprotein, apolipoprotein, lathosterol, hs-CRP, IL-6, and TNF-α concentrations and HOMA scores before and after treatment in the 48 obese participants studied are shown in Table 2. There were no significant interactions between atorvastatin and fish oil treatments for any of the variables. As expected, atorvastatin treatment had significant main effects of decreasing total cholesterol, triglycerides, LDL-C, apoB, and lathosterol and increasing HDL-C ($P <0.05$). Fish oil also had a significant main effect of lowering plasma triglycerides and increasing HDL-C ($P <0.05$). The HOMA score did not alter significantly on either atorvastatin or fish oil treatments.

The pre- and posttreatment plasma hs-CRP, IL-6, and TNF-α concentrations are shown in Fig. 1. Atorvastatin had a significant main effect of lowering plasma hs-CRP concentrations (-0.87 mg/L; 95% CI, -0.10 to -1.60 mg/L; $P <0.01$). This was paralleled by a significant reduction in plasma IL-6 concentrations with atorvastatin (-70 pg/L; 95% CI, 10 to -140 pg/L; main treatment effect, $P <0.01$). Plasma TNF-α concentrations did not alter significantly with atorvastatin or fish oil treatments. The average decrease in plasma CRP in patients treated with atorvastatin and atorvastatin plus fish oil was 40% ($P <0.05$), but the absolute concentrations remained significantly higher than in controls. In patients on placebo and fish oil, the mean change in plasma CRP was <2% ($P >0.05$). In the atorvastatin-treated groups, the change in CRP was not significantly correlated with other variables and particularly with plasma IL-6, LDL-C, lathosterol, insulin, or HOMA score.

Discussion

We confirmed that viscerally obese men have a significantly higher plasma concentration of hs-CRP than lean men, consistent with a low-grade chronic inflammatory state in obesity. The novel finding of our study was that treatment with atorvastatin was associated with significant reductions in plasma hs-CRP, but this was not seen
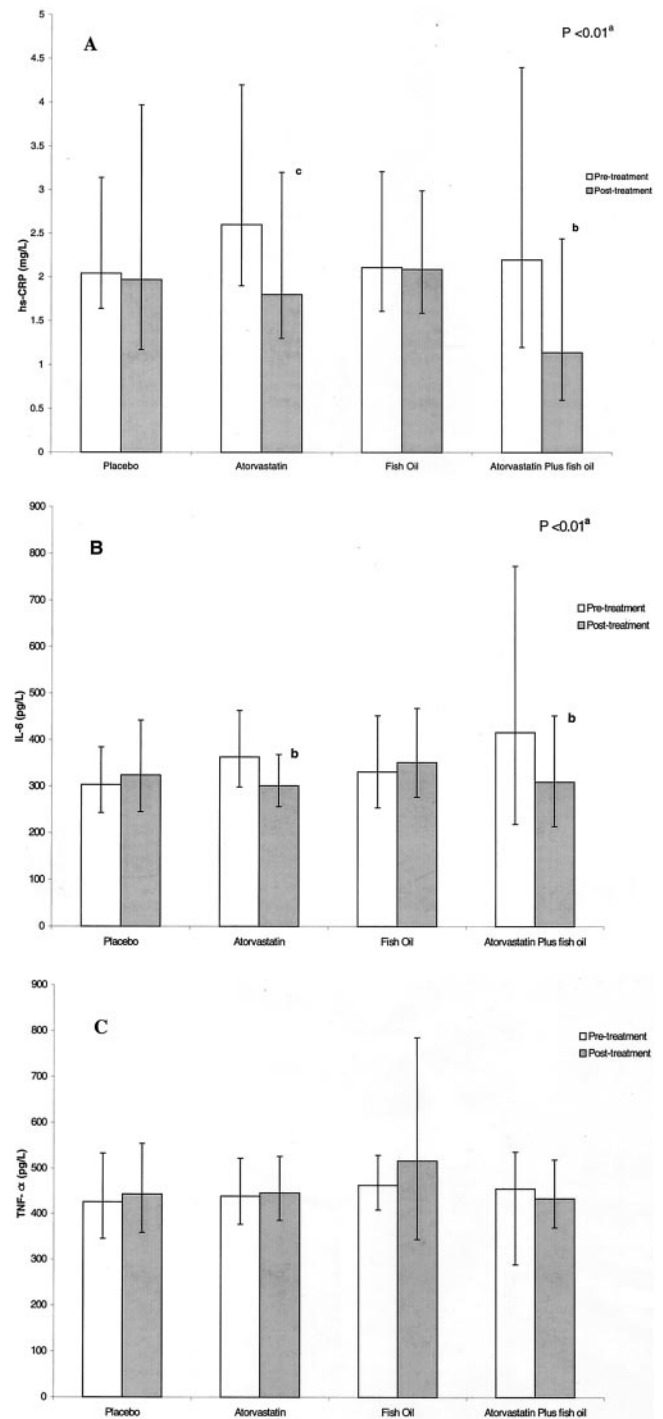

Fig. 1. Pre- (□) and posttreatment (▦) fasting plasma hs-CRP (A), IL-6 (B), and TNF-α (C) concentrations in the four groups.

Geometric means and 95% CIs (*error bars*) are shown. a, main treatment effect of atorvastatin was statistically significant; $P <0.01$. Significance within treatment group compared by *t*-test: b, $P <0.01$; c, $P <0.05$.

with fish oil treatment alone. The change in hs-CRP with atorvastatin was not related to changes in plasma lipids, insulin resistance, and rate of cholesterogenesis as measured by plasma lathosterol.

This is the first study to examine the antiinflammatory effects of atorvastatin and fish oil on plasma hs-CRP concentrations in obese individuals. Previous studies only examined the effect of statins on plasma hs-CRP in individuals with atherosclerosis or hyperlipidemia (22–25). None of these reports referred specifically to obesity. The effect of fish oil supplementation on plasma hs-CRP has surprisingly not been reported previously.

CRP may be associated with the initiation and progression of atherosclerotic disease by several mechanisms. These include enhancement of leukocyte reactivity, complement fixation, aggregation of lipoproteins, and modulation of platelet activation (26–28). The synthesis of CRP by the liver is largely regulated by the cytokine IL-6 (29). The activated leukocyte is widely assumed to be the major source of circulating IL-6 (30). Adipose tissue is also a major determinant for hs-CRP concentrations. Recent reports indicate that IL-6 is also produced by the adipocyte in vivo in proportion to fat mass (31). Thus, excess adiposity in obesity could increase the release of IL-6 from adipose tissue and may increase CRP expression. Energy restrictions and weight loss in obese individuals have been associated with a decrease in plasma hs-CRP (32). Furthermore, increased hs-CRP has been reported in diabetic patients, suggesting a link between hs-CRP and insulin resistance (33). Decreased insulin sensitivity may lead to enhanced CRP expression by counteracting the physiologic effect of insulin on hepatic acute-phase protein synthesis (34). Our results are consistent with the notion that increased plasma hs-CRP is associated with IL-6 concentrations and that a chronic low-grade inflammatory state is a feature of the metabolic syndrome of visceral obesity.

The precise antiinflammatory mechanism of statins in decreasing plasma hs-CRP in humans is not fully understood. However, several suggestions have been made in experimental studies that may explain the antiinflammatory effect of statins. These include inhibition of macrophage activity and subsequent production of cytokines and tissue factors (35) and reduction in inflammatory cell function by inhibition of matrix metalloproteinase activity (36). Consistent with the regulatory role of IL-6 on CRP synthesis (30), the significant reduction in plasma IL-6 concentrations with atorvastatin in our study may therefore partly account for the reduction in plasma hs-CRP concentrations. Statins may also reduce plasma hs-CRP concentrations by direct inhibition of CRP production through IL-6-independent mechanisms (37). Therefore, the absence of a significant association between changes in plasma hs-CRP and IL-6 concentrations with atorvastatin was not unexpected, particularly because we studied a relatively small sample size. Statin-induced inhibition of the Rho-signaling pathway may activate peroxisome proliferator-activated receptor-α and subsequently interfere with the mitogen-activated protein kinase cascade or nuclear factor-κB pathway; this may account for an antiinflammatory effect (38). Consistent with previous reports in other patient groups treated with other statins, our findings demonstrate that the major effect of atorvastatin was in decreasing plasma hs-CRP concentrations. Interestingly, this effect was independent of changes in the HOMA score and plasma lathosterol, suggesting mechanisms that may not directly involve alterations in insulin sensitivity or cholesterol synthesis. TNF-α is synthesized by adipocytes, and its metabolism is not as directly linked to CRP as that of IL-6. Hence, the absence of a significant decrease in TNF-α concentrations suggests that statins may have divergent effects on inflammatory pathways in obesity. That TNF-α did not alter with atorvastatin is also consistent with a lack of effect of atorvastatin on insulin resistance.

The synthesis of proinflammatory cytokines by peripheral monocytes has reportedly been suppressed by dietary fish oil supplementation (39). This suppression may therefore possibly lead to inhibition of CRP expression in the liver. In this study, fish oil supplementation alone had no significant effect on plasma hs-CRP in obese men. There are several possible explanations for our findings. For example, it is possible that small deleterious effects of fish oil on insulin sensitivity, as reflected by a small increase in the HOMA score (Table 2), might have stimulated CRP synthesis and counteracted the inhibitory effect of cytokines on CRP expression. Subtle changes in insulin sensitivity should preferably have been measured with a hyperinsulinemic, euglycemic clamp (40). Nevertheless, HOMA scores are well correlated with the clamp technique (19). We have shown in a factorial study that atorvastatin decreased both CRP and IL-6, but not TNF-α. This subacute effect may have implications for changes in arterial function and for acute coronary syndromes. The lack of effect of fish oil on plasma markers of inflammation in obesity was unexpected, but is a real result. We agree that a true treatment effect of fish oil might have been seen in a larger study. Such a study would have required a prohibitively large sample size, given that CRP decreased by only 2% with fish oil in our study.

The results of the present study are potentially clinically important. Low-grade chronic inflammation has been shown to be associated with increased risk of vascular disease. Recent epidemiologic studies have also demonstrated that plasma hs-CRP concentrations predict future coronary events among apparently healthy individuals (41). Our result showing that obese men have increased plasma hs-CRP concentrations may explain some of the increased risk of cardiovascular disease in obese individuals. Therefore, measurement of hs-CRP may be a potential marker for risk assessment in the primary prevention of CVD (42). Although not all clinical trials support the notion that statins potentially prevent diabetes (43), the West of Scotland Coronary Prevention Study Group has recently reported that statins reduce the incidence of type 2 diabetes (44) and that this may be related to its antiinflammatory effects. Because there is a close relationship between obesity and the development

of type 2 diabetes, the use of statins in treating dyslipidemia in visceral obesity may have additional benefits in the prevention or delay of the onset of diabetes in obese individuals. Our findings suggest that statins may be used as a first-line therapy for improving the plasma lipids profile as well as the chronic low-grade inflammatory state in obesity.

Although fish oil supplementation had no effect on plasma hs-CRP, the addition of fish oil to statins may further optimize the latter's lipid-regulating effects by enhancing a decrease in plasma triglycerides and increase in HDL-C. Because the posttreatment concentrations of plasma hs-CRP were not normalized, the incremental antiinflammatory effects of weight reduction (32), insulin sensitizers (45), fibrates (46), or aspirin (47) added to a statin may be required to correct this abnormality.

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