Energy Restriction and Weight Loss on Very-Low-Fat Diets Reduce C-Reactive Protein Concentrations in Obese, Healthy Women

L.K. Heilbronn, M. Noakes, P.M. Clifton

Abstract—C-reactive protein (CRP) is an inflammatory-response protein that is a strong, independent predictor of cardiovascular mortality. CRP is positively associated with body mass index (BMI). In this study, we investigated the effects of dynamic weight loss on CRP in 83 healthy, obese women (mean BMI, 33.8 ± 0.4 kg/m²; range, 28.2 to 43.8 kg/m²). Subjects were placed on very-low-fat, energy-restricted diets (5700 kJ, 15% fat) for 12 weeks. Weight, waist and hip circumferences, plasma lipids, glucose, and CRP were measured at baseline and after 12 weeks. CRP was positively associated with BMI (r = 0.281, P = 0.01) and waist circumference (r = 0.278, P = 0.01) but was not related to other atherosclerosis risk factors. BMI was significantly different between groups split above or below the median for CRP (34.8 ± 0.6 kg/m² vs 33.0 ± 0.5 kg/m², P = 0.02). After 12 weeks, weight loss was 7.9 ± 0.3 kg. CRP was significantly decreased by 26% (P < 0.001), and a correlation was observed between weight loss and the change in CRP (r = 0.309, P = 0.005). The variance in the change in CRP was partly explained by initial CRP (13.6%), energy intake (5.4%), and percentage weight loss (4.6%, P = 0.001). This study confirms recent observations that BMI is associated with CRP, a marker for low-grade systemic inflammation. Furthermore, we observed that CRP was lowered in proportion to weight loss. (Arterioscler Thromb Vasc Biol. 2001;21:968-970.)

Key Words: C-reactive protein ■ obesity ■ weight loss ■ moderate energy restriction

Atherosclerosis has been recognized as an inflammatory process. C-reactive protein (CRP) is an inflammatory-response protein that is elevated several hundred-fold in response to infection and is generally considered to be a good marker for inflammation. CRP usually exists at very low concentrations in plasma, with 90% of individuals having a CRP < 3.0 mg/L.1 Epidemiological studies suggest that CRP is a valuable risk marker for cardiovascular disease and that the addition of CRP to a plasma lipid level–based diagnosis may provide an improved method of identifying persons at risk for future cardiovascular events.2 However, it is unclear whether CRP is only a marker for disease progression or whether it is directly involved in the pathogenesis of atherosclerosis and whether reducing inflammation decreases the risk of myocardial infarction or stroke. However, the anti-inflammatory agent aspirin reduces CRP and the risk of myocardial infarction.3

See p 881

Longitudinal studies in which apparently healthy men and women were followed up for 3 to 8 years have shown that CRP, even at low plasma concentrations, is associated with a risk of cardiac events that is independent of lipid levels, smoking status, and body mass index (BMI).2,3 This finding suggests that inflammation is involved in the initiation of atherosclerosis. Men in the highest quintile of CRP (> 2.11 mg/L) had a 3-fold higher risk of myocardial infarction and a 2-fold increased risk of stroke compared with subjects in the lowest quintile of CRP (< 0.55 mg/L).3 CRP has also been positively associated with glucose, insulin resistance, total cholesterol, and triglyceride concentrations in men and women.3–6

CRP is also strongly associated with BMI.5–7 In a study that investigated >16 000 individuals, it was found that CRP was elevated (> 2.2 mg/L) in 60% of subjects with a BMI > 30 kg/m² compared with 35% of subjects with a BMI of 25 to 29.9 kg/m² and 20% of subjects with a BMI < 25 kg/m².7 Weight loss improves more traditional risk factor profiles for atherosclerosis, such as hypertension and hyperlipidemia.8 In this study, we examined CRP concentrations in obese women before and after 12 weeks of energy restriction and weight loss to determine whether CRP could be reduced by weight loss.

Methods

Subjects

Subjects were recruited by public advertisement that sought healthy women with a BMI > 28 kg/m². Subjects all had normal fasting

© 2001 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org
plasma glucose and lipid profiles (Table 1). Most subjects were sedentary at baseline and were requested to maintain their usual exercise habits throughout the study. This was assessed by an activity questionnaire each month. Twenty-eight women were postmenopausal, 13 of whom were taking hormone replacement therapy (HRT). Subjects gave written, informed consent to participate in the study, which was approved by the Human Ethics Committee of CSIRO, Health Sciences and Nutrition.

### Diets
Subjects were prescribed a 6.0-MJ diet that was restricted for fat intake (15% of total energy). Subjects were given detailed instructions for recording dietary intake and were required to complete detailed, 3-day dietary food records every 2 weeks. Dietary counseling and weight checks were also performed every 2 weeks. Overall, reported energy consumption was 5700±60 kJ/d. The macronutrient composition of the diet was 61.4±0.3% carbohydrate, 14.2±0.2% fat (saturated fat 5.9±0.1%), and 22.8±0.2% protein. Alcohol consumption was not allowed during the study.

### Design
Eighty-three nonsmoking, healthy, obese women (mean BMI, 33.8±0.4 kg/m²; range, 28.2 to 43.8 kg/m²) completed 12 weeks of energy restriction and weight loss, suggesting that weight loss is most likely due to interleukin-6 (IL-6). Il-6 is a strong, positive association between BMI and CRP.5–7 One study with a high CRP (33.0±0.5 vs 34.8±0.6 kg/m², *P*=0.02). BMI explained 7.7% of the variance in initial CRP (*P*=0.01).

No association was found between CRP and fasting plasma lipids or glucose concentrations at baseline. Furthermore, no significant differences were found in CRP at baseline between premenopausal (5.88±1.62 mg/L) and postmenopausal (5.01±1.12 mg/L) women, and adjusting for HRT did not affect these results.

After 12 weeks of energy restriction, total weight loss was 7.9±0.3 kg. Total cholesterol (−10%), LDL-C (−11%), HDL-C (−6%), and triglyceride (−14%) concentrations were significantly reduced. CRP was also significantly decreased from baseline (*P*<0.001, Table 2). The reduction in CRP was positively correlated with weight loss (*r*=0.270, *P*=0.001), percentage weight loss (*r*=0.309, *P*=0.005), and initial CRP value (*r*=0.347, *P*=0.001). No correlation was found between the change in CRP and reported energy intake (*r*=0.213, *P*=0.056). The variance in the change in CRP was explained by initial CRP (13.6%), energy intake (5.4%), and percentage weight loss (4.6%).

After weight loss, CRP was highly correlated with BMI (*r*=0.375, *P*=0.001) and indexes of fat mass (waist circumference [*r*=0.412, *P*=0.001] and hip circumference [*r*=0.379, *P*=0.001]). Furthermore, triglyceride and CRP concentrations were highly correlated (*r*=0.287, *P*=0.009), but total cholesterol, LDL-C, HDL-C, and glucose levels were not associated with CRP before or after weight loss. The change in CRP was also correlated with the change in total cholesterol (*r*=0.240, *P*=0.03) but not with the change in glucose, LDL-C, or HDL-C.

### Discussion
CRP is predictive of cardiac events,2,3 is associated with BMI in obese women, and is significantly reduced with moderate energy restriction and weight loss, suggesting that weight loss may reduce atherosclerotic risk.

In this study, baseline concentrations of CRP were higher than previously reported3 and may be reflective of the high level of obesity in this study group. Many studies have shown a strong, positive association between BMI and CRP.3–7 One previous study10 that examined CRP in 14 obese women reported concentrations of CRP (6.3 mg/L) similar to those in this study. The reason for the increased production of CRP in obesity is most likely due to interleukin-6 (IL-6). IL-6 is a

### Statistical Analysis
Statistical analysis was performed with SPSS for Windows, version 10 (SPSS, Inc). Significance was found by using a repeated-measures general linear model for weight-loss effects at weeks 0 and 12 and a 1-way ANOVA for all other tests. Correlations were performed by using Pearson’s correlation coefficient. All results are given as mean±SEM. Significance was set at *P*<0.05.

### Results
Characteristics of the population are described in Table 1. BMI ranged from 28.2 to 43.8 kg/m². At baseline, subjects had concentrations of total cholesterol, triglyceride, HDL-C, LDL-C, and glucose that were within normal healthy ranges (Table 2). CRP was elevated (mean, 5.5 mg/L; range, 0.24 to 15.76 mg/L), with 74% of subjects having CRP concentrations >3.0 mg/L. CRP was associated with BMI at baseline (*r*=0.281, *P*=0.01) and abdominal fat distribution as assessed by waist circumference (*r*=0.278, *P*=0.01) but not hip circumference or waist-hip ratio. The population was dichotomized into low and high CRP concentrations based on the median CRP (5.8 mg/L). Subjects with a low CRP had a significantly lower BMI at baseline compared with those with a high CRP (33.0±0.5 vs 34.8±0.6 kg/m², *P*=0.02). BMI explained 7.7% of the variance in initial CRP (*P*=0.01).

No association was found between CRP and fasting plasma lipids or glucose concentrations at baseline. Furthermore, no significant differences were found in CRP at baseline between premenopausal (5.88±1.62 mg/L) and postmenopausal (5.01±1.12 mg/L) women, and adjusting for HRT did not affect these results.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>83</td>
</tr>
<tr>
<td>Postmenopausal, n</td>
<td>28</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.0±0.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.8±0.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>98.3±1.0</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.83±0.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

### Table 2. Biochemical Characteristics Before and After Weight Loss

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.69±0.08</td>
<td>5.11±0.09*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.79±0.08</td>
<td>3.38±0.08*</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.15±0.03</td>
<td>1.08±0.03*</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.67±0.06</td>
<td>1.44±0.06*</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.90±0.07</td>
<td>4.79±0.05</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>5.56±0.36</td>
<td>4.12±0.36*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *

*P*<0.001 vs week 0.
cytokine that activates the production of CRP from the liver. Recent reports indicate that IL-6 is also produced by the adipocyte in vivo in proportion to fat mass.\textsuperscript{11} Thus, excess adiposity could increase expression of IL-6 and may increase CRP expression. Obesity-associated elevations in CRP may not, therefore, be related to higher inflammatory states or atherosclerotic progression. CRP has, however, been highly associated with the risk of cardiac events, independent of BMI,\textsuperscript{2,3,12} but the effects of CRP alone on cardiac events in obese populations have not been investigated.

We examined women only in this study, and women may have higher CRP concentrations in plasma than do men.\textsuperscript{13,14} The reason for the sex differences is unclear, although this could also be due to a higher percentage of body fat in women. This concept has not been investigated directly, because specific fat measurements were not taken. Garcia-Moll and colleagues\textsuperscript{15} found that even though CRP was higher in women, cardiac death rates were not different between the sexes.

We did not find any difference in CRP between premenopausal and postmenopausal women. This result has been supported by a larger study that investigated 186 women.\textsuperscript{5} However, a number of studies have found that CRP concentrations are \textasciitilde 2-fold higher in postmenopausal women on HRT compared with postmenopausal women not on HRT.\textsuperscript{1,15} We did not observe this association in postmenopausal women; however, only 13 women in the current study were using HRT.

CRP was reduced by 26\% after moderate weight loss and energy restriction, indicating a possible reduced risk of atherosclerosis. However, CRP concentrations were not normalized. This may have been due to the fact that more than half of the subjects were still classified as obese at week 12. CRP may have been reduced as IL-6 production from adipose tissue was reduced. The correlation between weight loss and CRP may have been reduced as IL-6 production from adipose tissue was reduced. This may have been due to the fact that more than half of the subjects were still classified as obese at week 12.

In summary, CRP is associated with BMI and waist circumference in obese women and was significantly reduced with weight loss, energy restriction, and a very-low-fat diet, indicating that the risk of cardiac events is reduced. However, further investigation into whether reductions in CRP are maintained during energy balance and prospective trials investigating weight loss, inflammatory state, and atherosclerotic disease progression are required.

References

Energy Restriction and Weight Loss on Very-Low-Fat Diets Reduce C-Reactive Protein Concentrations in Obese, Healthy Women
L. K. Heilbronn, M. Noakes and P. M. Clifton

doi: 10.1161/01.ATV.21.6.968

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/6/968

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/