Background: Adipose-derived cytokines, including tumor necrosis factor α, may contribute to the inflammation that occurs in the metabolic syndrome. We investigated the effects of inhibition of tumor necrosis factor α with etanercept in patients with the metabolic syndrome.

Methods: Fifty-six subjects with the metabolic syndrome were randomized to administration of either etanercept or identical placebo, 50 mg subcutaneously once a week for 4 weeks. The C-reactive protein level was the primary end point. Effects on other inflammatory markers (including fibrinogen, interleukin 6, and adiponectin), insulin sensitivity, lipid levels, and body composition were also determined.

Results: Baseline characteristics were similar between the groups. Two subjects dropped out of each group, and etanercept was well tolerated throughout the study. The C-reactive protein levels decreased significantly in the etanercept group compared with the placebo group (−2.4±0.4 vs −0.06±0.91 µg/mL; P=.04) and interleukin 6 levels tended to decrease (−1.2±0.8 vs 0.5±0.5 ng/L; P=.07) in the etanercept-treated subjects compared with placebo, respectively. No changes occurred in body composition parameters or insulin sensitivity, but high-density lipoprotein levels tended to decrease in the etanercept group (−1±1 vs 2±1 mg/dL [−0.03±0.03 vs 0.05±0.03 mmol/L]; P=.06) compared with the placebo group.

Conclusions: Etanercept reduces C-reactive protein levels and tends to improve other inflammatory cardiovascular risk indexes in patients with the metabolic syndrome. Etanercept may interrupt the inflammatory cascade that occurs with abdominal obesity. Further, longer-term studies are needed to determine the effects of tumor necrosis factor α inhibition on cardiovascular disease in patients with the metabolic syndrome.

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The prevalence of the metabolic syndrome ranges from 20% to 34% in 40- to 59-year-old men and women in the United States, and this rate is increasing.1 Evidence suggests a link among obesity, the metabolic syndrome, and coronary heart disease.2-4 The metabolic syndrome is thought to be a state of chronic inflammation, characterized by elevated levels of inflammatory cytokines, including tumor necrosis factor α (TNF-α).5 These cytokines are secreted by adipocytes and trigger an inflammatory cascade, resulting in increased C-reactive protein (CRP) level and a reduced adiponectin level.6,7 Inflammation may contribute to increased coronary artery disease risk in patients with the metabolic syndrome.5,8,9 Secretion of TNF-α by omental adipocytes is one potential mechanism that links excess fat and cardiovascular disease. Prior studies have demonstrated a significant relationship between TNF-α and recurrent myocardial infarction rates. Studies have shown that TNF-α can induce secretion of interleukin 6 (IL-6), which then acts as a potent stimulant of hepatic production of CRP. Recent in vitro data have suggested that TNF-α may decrease adiponectin secretion.13 A treatment strategy to inhibit the activity of TNF-α may improve inflammatory risk indexes in patients with abdominal obesity and the metabolic syndrome.

Etanercept is a dimeric recombinant form of the extracellular domain of the human p75 TNF-α receptor 2 fused to the Fc fragment of human immunoglobulin G1 (IgG1) used to treat inflammatory arthritis. Etanercept acts as a TNF-α antagonist by interfering in the binding of TNF-α to its cellular receptors and thus blocks the inflammatory response. We conducted a randomized, placebo-controlled study to assess the effects of etanercept administration on CRP as a primary end point in patients with the metabolic syndrome.

METHODS

PARTICIPANTS

Eligible subjects between the ages of 18 and 55 years were seen at the General Clinical Re-
search Centers of the Massachusetts General Hospital (MGH) and the Massachusetts Institute of Technology (MIT) and met the modified World Health Organization (WHO) criteria of metabolic syndrome with either hyperinsulinemia (insulin, $\geq 10 \mu U/mL \ [\geq 69.5 \text{ pmol/L]}) or impaired glucose tolerance (fasting glucose, 110-129 mg/dL [6.11-6.94 mmol/L] and 2 of 3 additional criteria: (1) waist-to-hip ratio (WHR) greater than 0.90 for men and greater than 0.85 for women or body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) greater than 30, (2) serum triglyceride level of 150 mg/dL or higher (\(\geq 1.70 \text{ mmol/L}) or high-density lipoprotein cholesterol level less than 35 mg/dL (\(<0.91 \text{ mmol/L}) for men and less than 39 mg/dL (\(<1.01 \text{ mmol/L}) for women, and (3) blood pressure of 140/90 mm Hg or higher or receiving antihypertensive medication.

Subjects were excluded if they had a history of known coronary artery disease or diabetes mellitus and/or were taking insulin or any antihyperglycemic medication, niacin or fibrates, or immunosuppressant medication, including oral steroids. Those with a history of chronic infection (including tuberculosis, human immunodeficiency virus, and chronic hepatitis), malignancy, organ transplantation, blood dyscrasia, congestive heart failure classes I to IV, central nervous system demyelinating disorder, and any other known autoimmune or inflammatory condition or a positive pregnancy test result were also excluded. Purified protein derivatives 5 tuberculin units were intradermally placed at the screening visit, and all patients with a reaction greater than 5 mm were excluded. All subjects gave written informed consent, and the study was approved by the Human Research Committee of the MGH, the Committee on the Research of Human Subjects at MIT, and the Food and Drug Administration (investigational new drug No. 11463).

**INTERVENTIONS**

**Screening Visit**

Subjects underwent a screening evaluation, including assessment of WHR, BMI, fasting insulin and glucose levels, lipid levels, blood pressure, purified protein derivative status, and medical history to determine eligibility.

**Baseline Visit**

Eligible subjects willing to participate were enrolled and returned for a baseline visit. Subjects arrived in the morning after an overnight fast. Height, weight, WHR, and BMI were determined. A 24-hour food recall was obtained. Fasting blood was drawn for concentrations of glucose, insulin, CRP, adiponectin, IL-6, TNF-\(\alpha\), soluble TNF-\(\alpha\) receptor 1 (sTNFR1), soluble TNF-\(\alpha\) receptor 2 (sTNFR2), fibrinogen, and free fatty acids; a lipid panel; and complete blood cell count. Subjects underwent an insulin-modified, frequently sampled, intravenous glucose tolerance test. A single-slice cross-sectional computed tomographic scan of the abdomen and a total-body dual-energy x-ray absorptiometry scan were performed.

**Dosing**

After the baseline visit was complete, subjects were randomized to receive either etanercept (Enbrel; Amgen Inc, Thousand Oaks, Calif), 50 mg subcutaneously weekly in two 25-mg injections, or identical placebo, one immediately following the other, at different body sites. The study drug was stored at the MGH research pharmacy at 2°C to 8°C before reconstitution and was administered by the General Clinical Research Center (GCRC) nursing staff. The blinded study drug was supplied in 2 single-use vials and was reconstituted with sterile water immediately before subcutaneous injection. The dosing was identical to that recommended for patients with rheumatoid arthritis. Subjects were monitored for 30 minutes after the injection of the study drug before discharge.

**Subsequent Visits**

Subjects returned for 3 more weekly visits on study days 8, 15, and 22 for a physical examination, interval history, and blood work, including a white blood cell count for safety monitoring, testing for inflammatory markers, and a pregnancy test for female patients. Nurses administered the weekly dose of etanercept (30 mg) or placebo in divided subcutaneous doses, as at the baseline visit. On day 25, 3 days after the fourth and final dose of the study drug, subjects returned for a final visit and underwent testing identical to baseline.

**Insulin Sensitivity**

The frequently sampled, intravenous glucose tolerance test was used to measure insulin sensitivity. Venous blood was frequently sampled for glucose and insulin. Insulin sensitivity was calculated using the Minimal Model (version 3.0; Min-Mod Inc, Los Angeles, Calif, 1994).

**Body Composition**

Whole-body dual-energy x-ray absorptiometry was performed to assess fat and lean mass (Hologic 4500; Hologic Inc, Waltham, Mass). In our laboratory, the technique has a precision error of 1.7% for fat and 2.4% for lean mass. Cross-sectional abdominal computed tomographic scanning at the L4 pedicle was performed to assess subcutaneous and visceral abdominal fat areas.

**Laboratory Analysis**

All samples from the same patient were run in duplicate in the same assay. Levels of CRP were measured by enzyme-linked immunosorbent assay (intra-assay coefficient of variation [CV] of 1.7%-3.9%; sensitivity, 0.002 mg/L; Diagnostic Systems Laboratories Inc, Webster, Tex). Adiponectin was measured by radioimmunoassay (CV, 1.8%-3.6%; sensitivity, 0.001 µg/mL; LINCO Research Inc, St Charles, Mo). Sandwich enzyme immunoassay technique was performed for TNF-\(\alpha\) (CV, 5.3%-8.8%; sensitivity, 0.12 pg/mL), sTNFR1 (CV, 3.6%-5.0%; sensitivity, 0.001 ng/mL), sTNFR2 (CV, 2.6%-4.8%; sensitivity, 0.001 ng/mL), and IL-6 (CV, 6.9%-7.8%; sensitivity, 0.039 ng/mL) using kits from R&D Systems Inc, Minneapolis, Minn. Insulin was measured by radioimmunoassay (CV, 4.9%-10%; Diagnostic Products Corp, Los Angeles, Calif). The concentration of fibrinogen (CV, <1.50%) was determined using an immunoturbidimetric assay with reagents and calibrators from Kamiya Biomedical Co (Seattle, Wash). Nonesterified fatty acid concentrations were measured using an in vitro enzymatic colorimetric assay kit (CV, 1.1%-2.7%; Wako Chemicals USA Inc, Richmond, Va). Complete blood cell count and glucose and lipid concentrations were measured by standard technique.

**Objectives**

We hypothesized that inhibition of TNF-\(\alpha\) with etanercept would reduce elevated inflammatory indexes in patients with the metabolic syndrome. The purpose of the study was to determine the effects of etanercept on inflammatory and metabolic indexes in patients with the metabolic syndrome.
Outcomes

The primary outcome was CRP level. The secondary outcomes were other inflammatory markers, including adiponectin, fibrinogen, and IL-6 levels, and other metabolic variables, including insulin sensitivity and lipid levels.

Sample Size

The study was powered at 80% using a 2-tailed, 2-sample t test at the .05 significance level to detect a 3.2-mg/L change in CRP for a sample size of 50 patients. Fifty-six patients were recruited to account for a projected discontinuation rate of 10%.

Randomization and Blinding

All subjects were enrolled by a study physician. The MGH Research Pharmacy performed the randomization based on sequential enrollment numbers using a permuted block algorithm and kept the randomization code. Randomization was stratified by sex. The allocation was concealed, and the blinded study drug or placebo was dispensed for each visit. All investigators, study staff, and subjects were blinded to drug assignment throughout the entire study.

STATISTICAL ANALYSIS

Baseline comparisons were made with the t test or the χ² test for categorical variables. For inflammatory indexes, assessed weekly throughout the study, a mixed-model regression was used to determine the treatment effect of etanercept vs placebo with time. Effects of BMI in the model were also tested. For other data, assessed at baseline and the end of the study, the treatment effect over time of etanercept vs placebo was determined using analysis of covariance, in which the end of study value was the dependent variable, and the randomization effect was tested, controlling for baseline value as a covariate. Similar results were obtained with statin use as a covariate. Statistical significance was defined as a 2-tailed α value of <.05. Statistical analysis was made using JMP for SAS (SAS Institute Inc, Cary, NC). Results are reported as mean±SEM unless otherwise indicated.

RESULTS

RECRUITMENT

One hundred sixty-four subjects were screened; 90 were ineligible, 18 declined to participate, and 56 patients were randomized (28 to etanercept and 28 to placebo). Two subjects withdrew in each group (Figure 1). Subjects were recruited between April 2004 and March 2005 using community advertisements.

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

The age of the study population was 45.6±8.4 years, BMI was 36.5±5.5, and WHR was 0.96±0.07 (mean±SD). Of the 56 subjects randomized, 30 were male and 26 female, and the sex distribution was equivalent. Fifteen subjects were receiving statins, and 31 were receiving antihypertensive medication, and these percentages did not differ between the treatment groups. No subjects were receiving hormone replacement therapy. No subject began a new lipid-lowering agent during the study. Baseline characteristics, including inflammatory indexes, were not significantly different in the 2 groups (Table 1 and Table 2), but BMI and CRP level tended to be higher in the etanercept group at baseline. Subjects were in-

Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 28)</th>
<th>Etanercept (n = 28)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.2 ± 8.3</td>
<td>45.1 ± 8.7</td>
<td>.64</td>
</tr>
<tr>
<td>WHR</td>
<td>0.96 ± 0.07</td>
<td>0.96 ± 0.06</td>
<td>.87</td>
</tr>
<tr>
<td>BMI</td>
<td>35.1 ± 4.8</td>
<td>37.9 ± 5.9</td>
<td>.05</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19</td>
<td>18</td>
<td>.24</td>
</tr>
<tr>
<td>Black/African American</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>15</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>98 ± 18</td>
<td>93 ± 13</td>
<td>.31</td>
</tr>
<tr>
<td>Fasting insulin, µIU/mL‡</td>
<td>17.0 ± 9.7</td>
<td>24.1 ± 25.3</td>
<td>.21</td>
</tr>
<tr>
<td>Fasting HDL-C, mg/dL</td>
<td>40 ± 9</td>
<td>39 ± 9</td>
<td>.66</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125 ± 13</td>
<td>131 ± 19</td>
<td>.52</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82 ± 10</td>
<td>82 ± 13</td>
<td>.94</td>
</tr>
<tr>
<td>Antihypertensive drug use</td>
<td>18</td>
<td>13</td>
<td>.18</td>
</tr>
<tr>
<td>Statin use</td>
<td>9</td>
<td>6</td>
<td>.36</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>5.1 ± 3.5</td>
<td>7.0 ± 3.9</td>
<td>.07</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>7.6 ± 3.6</td>
<td>7.0 ± 3.5</td>
<td>.35</td>
</tr>
<tr>
<td>Interleukin 6, ng/L</td>
<td>4.5 ± 3.5</td>
<td>5.0 ± 4.3</td>
<td>.68</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>443 ± 109</td>
<td>439 ± 108</td>
<td>.91</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; WHR, waist-hip ratio.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; to convert insulin to picomoles per liter, multiply by 6.945; to convert HDL-C to millimoles per liter, multiply by 0.0259; to convert fibrinogen to micromoles per liter, multiply by 0.0294.

*Data are presented as mean±SD unless otherwise indicated.
†P-value for comparison at baseline by t test.
‡Insulin reference range is less than 15 µIU/mL (<104 pmol/L).
included based on the modified WHO criteria for the metabolic syndrome. Using the conventional Ford criteria and the updated Ford criteria, 82% and 84%, respectively, of our study population would be classified as having the metabolic syndrome.

EFFECTS OF ETANERCEPT ADMINISTRATION

Inflammatory Indexes

Levels of CRP decreased in the etanercept group compared with the placebo group (−2.4±0.4 vs 0.5±0.7 mg/L, respectively; P<.001. Adiponectin levels increased in the etanercept-treated subjects compared with the placebo group (0.8±0.4 vs −0.3±0.3 µg/mL; P=.03). Fibrinogen levels decreased (−68±16 vs −2±31 mg/dL [−2.0±0.47 vs −0.06±0.91 µmol/L]; P=.04) and IL-6 levels tended to decrease (−1.2±0.8 vs 0.5±0.5 ng/L; P=.07) in the etanercept-treated subjects compared with the placebo group (Figure 2 and Table 2).

Similar results were obtained including BMI in the analysis (data not shown).

Figure 2. Changes in C-reactive protein (CRP) levels. Results are presented as mean±SEM (error bars). *P<.001 for comparison of treatment effect from baseline (etanercept vs placebo) using a mixed-model analysis for longitudinal data.

TNF-α Receptors

Although sTNFR1 level did not change significantly, sTNFR2 level increased significantly in the etanercept group.

Table 2. Clinical End Points*

<table>
<thead>
<tr>
<th>End Points</th>
<th>Placebo (n = 28)</th>
<th>Change From Baseline</th>
<th>Etanercept (n = 28)</th>
<th>Change From Baseline</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>5.1 ± 0.7</td>
<td>0.5 ± 0.7</td>
<td>7.0 ± 0.7</td>
<td>−2.4 ± 0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>7.6 ± 0.7</td>
<td>−0.3 ± 0.3</td>
<td>7.0 ± 0.7</td>
<td>0.8 ± 0.4</td>
<td>.03</td>
</tr>
<tr>
<td>Interleukin 6, ng/L</td>
<td>4.5 ± 0.7</td>
<td>0.5 ± 0.5</td>
<td>5.0 ± 0.8</td>
<td>−1.2 ± 0.8</td>
<td>.07</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>443 ± 21</td>
<td>−2 ± 31</td>
<td>439 ± 20</td>
<td>−68 ± 16</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Body composition and nutritional parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>35.1 ± 0.9</td>
<td>0 µ ± 0.1</td>
<td>37.9 ± 1.1</td>
<td>−0.0 ± 0.1</td>
<td>.54</td>
</tr>
<tr>
<td>Total fat, kg</td>
<td>38.0 ± 2.1</td>
<td>0.1 ± 0.2</td>
<td>40.7 ± 2.8</td>
<td>−0.0 ± 0.2</td>
<td>.66</td>
</tr>
<tr>
<td>Total lean mass, kg</td>
<td>64.0 ± 2.5</td>
<td>−0.2 ± 0.3</td>
<td>67.3 ± 2.4</td>
<td>−0.1 ± 0.3</td>
<td>.87</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>201.9 ± 13.4</td>
<td>0.2 ± 7.0</td>
<td>213.8 ± 15.0</td>
<td>2.7 ± 6.1</td>
<td>.76</td>
</tr>
<tr>
<td>Total caloric intake, kcal/d</td>
<td>2172 ± 163</td>
<td>−142 ± 230</td>
<td>2201 ± 182</td>
<td>−34 ± 157</td>
<td>.73</td>
</tr>
<tr>
<td>Total fat intake, g/d</td>
<td>88 ± 10</td>
<td>−7 ± 12</td>
<td>95 ± 9</td>
<td>−1 ± 9</td>
<td>.60</td>
</tr>
<tr>
<td><strong>Lipids and insulin sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>40 ± 2</td>
<td>2 ± 1</td>
<td>39 ± 2</td>
<td>−1 ± 1</td>
<td>.06</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>117 ± 8</td>
<td>−1 ± 4</td>
<td>121 ± 5</td>
<td>−6 ± 4</td>
<td>.55</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>190 ± 8</td>
<td>1 ± 5</td>
<td>189 ± 6</td>
<td>−4 ± 4</td>
<td>.54</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>206 ± 36</td>
<td>−5 ± 39</td>
<td>199 ± 36</td>
<td>−14 ± 25</td>
<td>.75</td>
</tr>
<tr>
<td>FFA, mEq/L</td>
<td>0.5 ± 0.0</td>
<td>0 ± 0.0</td>
<td>0.6 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>.93</td>
</tr>
<tr>
<td>S1, ×10⁻⁴·min⁻¹·µIU per mL</td>
<td>1.90 ± 0.36</td>
<td>0.76 ± 0.34</td>
<td>1.52 ± 0.23</td>
<td>0.33 ± 0.20</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Safety parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, 10³/µL</td>
<td>6.6 ± 0.4</td>
<td>−0.2 ± 0.4</td>
<td>6.5 ± 0.3</td>
<td>−0.6 ± 0.3</td>
<td>.35</td>
</tr>
<tr>
<td>TNF-α receptors, ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sTNFR1</td>
<td>1.33 ± 0.08</td>
<td>−0.03 ± 0.06</td>
<td>1.33 ± 0.08</td>
<td>0.02 ± 0.05</td>
<td>.56</td>
</tr>
<tr>
<td>sTNFR2</td>
<td>2.78 ± 0.19</td>
<td>−0.19 ± 0.13</td>
<td>2.99 ± 0.25</td>
<td>7.68 ± 0.42</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SI, insulin sensitivity; sTNFR1, soluble TNF-α receptor 1; sTNFR2, soluble TNF-α receptor 2; TNF-α, tumor necrosis factor α; VAT, visceral adipose tissue; WBC, white blood cell count.

*P values for comparison at baseline by t test all greater than .05.
†P values for comparison of treatment effect from baseline (etanercept vs placebo) for C-reactive protein, adiponectin, interleukin 6, and sTNFR2 by mixed-model analysis. P value for comparison of treatment effect from baseline (etanercept vs placebo) for all other variables by analysis of covariance. P values for comparison of treatment effect from baseline (etanercept vs placebo) by mixed-model analysis for longitudinal data.

‡Fibrinogen reference range is 200 to 400 mg/dL (5.9-11.8 µmol/L).

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group compared with the placebo group (Table 2). The change in sTNFR2 level correlated significantly with the change in CRP ($r = -0.31; P = .02$) and adiponectin ($r = 0.42; P = .002$).

**Insulin Sensitivity, Body Composition, Lipids Concentrations, and Nutritional Status**

Changes in BMI, WHR, total fat and visceral adipose tissue, insulin sensitivity, and nutritional status did not differ significantly between the groups (Table 2). Total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels did not change between groups, but high-density lipoprotein levels tended to decrease in the etanercept group ($-1\pm1$ vs $2\pm1$ mg/dL; $-0.03\pm0.03$ vs $0.05\pm0.03$ mmol/L; $P = .06$) compared with the placebo group.

**Adverse Events**

Etanercept was well tolerated throughout the study. In the etanercept group, 1 subject with a borderline low white blood cell count at baseline before taking the medication discontinued study participation because of a slight decrease in his white blood cell count after his second visit. White blood cell count, however, did not change significantly between the study groups (Table 2). A second subject in the etanercept group discontinued study participation because of a psychiatric illness likely unrelated to the drug after the first visit. In an additional subject in the etanercept group, a transient asymptomatic rash was noted at the injection sites after the third visit that resolved spontaneously the following week. The patient remained in the study. Compliance was 100% for those in the study, because the study drug was always administered by the GCRC nursing staff.

**COMMENT**

Recent data suggest that inflammation from adipocyte-derived cytokines may contribute to the development of atherosclerosis. Our data from a randomized, placebo-controlled study demonstrate that inhibition of TNF-α with etanercept improves abnormal inflammatory cardiovascular risk indexes in patients at high risk for cardiovascular disease with the metabolic syndrome.

Based on 2000 US Census data, an estimated 47 million Americans have the metabolic syndrome. Cardiovascular disease morbidity and mortality are increased among patients with the metabolic syndrome. Among patients with the metabolic syndrome, inflammatory risk markers, including CRP, are elevated and associated with cardiovascular disease. Baseline CRP levels were increased at 6.1 mg/L, similar to the data of Malik et al$^{10}$ from a large cohort of patients with the metabolic syndrome. Furthermore, subjects with other known inflammatory conditions were excluded from our study, suggesting that increased inflammation and CRP were linked to an obesity-associated activation of the TNF system. This paradigm differs from prior studies of patients with known inflammatory conditions, including ankylosing spondylitis,$^{31}$ rheumatoid arthritis,$^{22}$ and psoriatic arthritis,$^{23}$ in which etanercept has been shown to decrease CRP levels and improve endothelial function.$^{24}$

In this study we used a well-validated WHO definition of the metabolic syndrome.$^{2,14,15}$ Among patients with metabolic syndrome, cardiovascular disease is higher in patients with intermediate and high CRP levels than in patients with low CRP levels, controlling for other cardiovascular risk factors.$^{25}$ Prior studies have shown that patients with the metabolic syndrome and a CRP level greater than 3 mg/L have a cardiovascular disease risk equal to the risk in patients with diabetes with a CRP level less than 1 mg/L.$^{20}$ In this study, etanercept administration decreased CRP by more than 2 mg/L, representing a 34% reduction after 4 weeks. Weight, nutritional status, and body composition did not change, suggesting an independent effect of etanercept to improve CRP.

Adiponectin is an adipocyte-derived cytokine, which has anti-inflammatory and antiatherosclerotic properties and is decreased in obese populations.$^{10}$ Reduced adiponectin concentrations have been found to be predictive of the development of coronary artery disease,$^{26}$ potentially through effects on the endovasculature.$^{27}$ In vitro and animal studies suggest that adiponectin may reduce inflammation and cell adhesion at the endothelial surface,$^{28}$ decrease foam cell formation through effects on scavenger uptake by macrophages,$^{29}$ and inhibit proliferation and migration of smooth muscle cells.$^{30}$ In several in vitro studies, TNF-α has been shown to decrease adiponectin secretion from differentiated adipocytes and preadipocytes.$^{13}$ In this study we show that inhibition of TNF-α significantly increases adiponectin in patients with the metabolic syndrome.

Interleukin 6 is stimulated by several factors, including TNF-α,$^{12}$ and has been prospectively associated with cardiovascular risk.$^{31,32}$ Increased production of IL-6 by adipocytes in patients with abdominal obesity may further stimulate hepatic CRP production. The TNF-α antagonists decrease IL-6 levels in patients with rheumatoid and juvenile arthritis.$^{33,34}$ Etanercept has also been shown to decrease IL-6 levels in overweight patients with sleep apnea.$^{35}$ Inhibition of TNF-α tended to reduce IL-6 levels in our study of subjects with the metabolic syndrome.

In addition to effects on CRP and adiponectin, inhibition of the TNF system may reduce other inflammatory pathways. Fibrinogen is a clotting factor and marker of inflammation and abnormal hemostasis. Fibrinogen was markedly increased at baseline among our subjects with the metabolic syndrome. Fibrinogen is thought to be an independent mediator of cardiovascular disease$^{36}$ and decreased significantly in response to etanercept.

In addition, TNF-α may also affect glucose homeostasis.$^{37}$ Infusion of a TNF receptor–IgG fusion protein improved insulin sensitivity in mice,$^{38}$ but subsequent studies in human diabetic and obese patients using single doses of TNF-α receptor 1 antagonists failed to detect changes in insulin sensitivity.$^{39,40}$ A recent study in patients with type 2 diabetes mellitus did not show an improvement in insulin sensitivity.$^{41}$ In our study, a 4-week course of etanercept did not change insulin sensitivity in a highly insulin-resistant population without overt diabetes mellitus. The absence of an effect on insulin sen-
sitivity may be due to dosing duration, the choice of population, or the presence of more powerful determinants of insulin sensitivity. Alternatively, these data suggest a potential dissociation between TNF-α-mediated effects on inflammation and insulin resistance in humans.

Tumor necrosis factor α resulted in significant increases in sTNFR2 level. Etanercept is a dimeric fusion protein between the recombinant form of the human p75 TNF-α receptor 2 and the Fc fragment of human IgG1 and is therefore measured in the assay for native sTNFR2. The increase in sTNFR2 level correlated with the reduction in CRP and increase in adiponectin, suggesting that this increase may be a marker for the effects of TNF-α inhibition with etanercept. Prior studies41,42 have shown an increase in TNF-α in response to TNF inhibition with etanercept. An increase in measured TNF-α was also seen in this study (data not shown) and likely relates to the facts that etanercept sequesters TNF-α in the circulation and both free TNF and that bound to the sTNFR2 are measured in the TNF-α assay.

Etanercept was safe throughout 4 weeks in patients with the metabolic syndrome strictly screened for contraindications to this drug. Etanercept is known to potentially impair immune function, and subjects with a history of chronic infection were excluded. Etanercept is not approved by the Food and Drug Administration for the treatment of inflammation in patients with the metabolic syndrome, and further studies with longer duration will be necessary to determine safety in this population.

This study had several limitations. The sample size was relatively small, and the dosing duration was short term. Both BMI and CRP levels tended to be greater at baseline in the etanercept group, but results were not affected when BMI was included in the mixed regression modeling, accounting for baseline values. The study was powered on the primary end point, CRP, which was highly significant. More marginal treatment effects were seen in other inflammatory indexes, such as fibrinogen, adiponectin, and IL-6. In contrast, high-density lipoprotein cholesterol levels tended to decrease more in the etanercept-treated group. The clinical significance of these results remains unclear.

Our data demonstrate an effect of TNF-α inhibition to reduce CRP levels and potentially modify other inflammatory cytokines in patients with the metabolic syndrome. These data suggest a novel and physiologically relevant approach to improve the increased inflammatory milieu associated with abdominal obesity, but further studies are necessary to investigate the overall effects of longer-term etanercept administration on cardiovascular disease.

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Correspondence: Steven K. Grinspoon, MD, MGH Program in Nutritional Metabolism, 55 Fruit St, LON 207, Boston, MA 02114 (sgrinspoon@partners.org).

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