High-Sensitivity C-Reactive Protein in Patients with Metabolic Syndrome

Aytekin Guven, MD,[1] Ali Cetinkaya, MD,[2] Murat Aral, MD,[3] Gulizar Sokmen, MD,[1] Mehmet Akif Buyukbese, MD,[2] Alanur Guven, MD,[4] and Nurhan Koksal, MD,[5]
Kahramanmaraş, Turkey

High-sensitivity C-reactive protein (CRP) has been shown to predict cardiovascular disease. Metabolic syndrome has been found to play a critical role in the development of cardiovascular disease. The purpose of this report is to assess the relationship between CRP and the metabolic syndrome. A total of 50 patients with metabolic syndrome and 40 healthy persons were included in the study. Plasma concentrations of CRP were measured by means of particle-enhanced immunonephelometry with the Behring nephelometer using N Latex CRP mono reagent. CRP levels were higher in patients with metabolic syndrome than control group (10.6 ±5.4 mg/L vs 3.5 ±0.8 mg/L, $p < 0.001$). In partial correlation, plasma CRP positively correlated with body mass index ($p < 0.001$), waist circumference ($p < 0.001$), waist-to-hip ratio ($p < 0.01$), total cholesterol ($p < 0.001$), LDL-cholesterol ($p = 0.033$), triglyceride ($p = 0.023$), and fasting blood glucose ($p = 0.043$) in patients with metabolic syndrome. HDL-cholesterol did not significantly correlate with CRP ($p > 0.05$). In multiple regression analysis, body mass index ($p < 0.01$), waist circumference ($p < 0.01$), and fasting blood glucose ($p < 0.01$) showed independent correlations with plasma CRP. CRP levels were found higher in patients with metabolic syndrome. These results suggest that abdominal obesity is the critical correlates of elevated plasma CRP levels found in patients with metabolic syndrome. These patients carrying high risk for cardiovascular events must be followed closely.

Introduction

Inflammation is thought to play an important role in the progression and complications of atherosclerosis.[1-5] Hence, several markers of inflammation have been evaluated in the previous years. C-Reactive protein (CRP), a nonspecific marker of inflammation, has been proven to be one of the strongest predictors of the risk of cardiovascular disease, as well as in patients without cardiovascular disease.[6,7-9] CRP is an acute phase reactant expressed principally by the liver. In healthy, lean individuals CRP circulates at low concentrations in plasma (< 3 mg/L). These levels increase dramatically in response to injury, in-

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From the Departments of [1]Cardiology, [2]Internal Medicine, [3]Clinical Microbiology, [4]Gynecology and Obstetric Disease, and [5]Pulmonary Disease, Kahramanmaraş Sutçu Imam University School of Medicine, Kahramanmaraş, Turkey

Correspondence: Aytekin Guven, MD, Kahramanmaraş Sutçu Imam Universitesi, Tıp Fakultesi Kardiyoloji ABD, 46050 Kahramanmaraş, Turkey
E-mail: aytekinguven@hotmail.com

fection and inflammation, in response to bacterial lipopolysaccarides, interleukin-1β, intreleukin-6, oncostatin M, and leukemia inhibitory factor.[10,11] Slightly increased CRP concentrations, detected with high sensitivity kits, but still within what has traditionally been regarded as the normal range (1–10 mg/L) may reflect chronic low-grade inflammation.[12]

Metabolic syndrome is a clinical syndrome in which multiple risks are clustered in an individual and is a common basis of vascular disease in the industrial countries. Metabolic syndrome, dysmetabolic syndrome or insulin-resistance syndrome (or syndrome X as it was initially designated), which is closely linked to insulin resistance, is a condition that is recognized as increasing the risk of cardiovascular disease.[13,14] It was originally described by Reaven as quartet of hypertension, glucose intolerance, and dyslipidemia (high triglyceride, low high-density lipoprotein-cholesterol (HDL-cholesterol), with insulin resistance or hyperinsulinemia. Central obesity is often associated and other phenotypes, such as impaired fibrinolysis, microalbuminuria, small dense low-density lipoprotein (LDL) particles and markers of acute phase reactants, were later found to be associated.[14-16] The risk of atherosclerosis is increased in patients with metabolic syndrome.

There is growing evidence that local and perhaps systemic inflammation is involved in the initiation and progression of atherosclerosis.[17] Numerous studies have observed increased levels of CRP and other inflammatory markers in apparently healthy subjects in whom acute vascular events develop.[18] The risk for development of cardiovascular events is higher in patients with metabolic syndrome. Thus, we aimed to investigate CRP levels, a strong inflammatory marker, in patients with metabolic syndrome.

Methods

Study Population

A total of 42 men and 48 women formed the study population. All subjects provided informed consent. A very detailed examination was done to eliminate the asymptomatic chronic or acute infections. The program included the taking of full medical history and physical examinations, urinalysis, blood cell counts, blood chemistry, a glucose tolerance test, serologic tests for hepatitis viruses, a chest radiograph, an electrocardiogram, a respiratory function, an alimentary examination of the upper gastrointestinal tract, and abdominal ultrasonography. The physical examination was performed by a cardiologist, internist, surgeon, ophthalmologist, otorhinolaryngologist, dentist, and a gynecologist for women.

Patients with coronary heart disease, significant valvular disease, diabetes mellitus, life-threatening systemic disease, chronic obstructive pulmonary disease, and smokers were not enrolled into the study.

Measurement of Risk Factors and Validation

Blood pressure was measured in the sitting position on the right arm using a sphygmomanometer (Erka, Germany), after at least 10 minutes of rest. First appearance and disappearance (phase V) of Korotkoffs sounds were used to define the pressures. Readings were recorded to the nearest even number, and the mean of 2 recordings 3 minutes apart was computed. Waist circumference was measured with the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest, while that of the hip was measured at the level of the greater trochanters. Body mass index (BMI) was calculated by a computer as weight divided by height squared (kg/m^2).

Blood samples were taken from all subjects between 8 and 10 AM after a 14-hour overnight fast. Plasma concentrations of cholesterol, fasting triglycerides, HDL-cholesterol, and glucose were determined by the enzymatic dry chemistry method using a Behring apparatus. LDL-cholesterol values were computed according to the Friedewald formula.

The definition of the metabolic syndrome was as recommended by the National Cholesterol Education Program,[19] and was considered present if the subject had 3 of the following factors: waist circumference > 102 cm (men) or > 88 cm (women), triglyceride level ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women), blood pressure $\geq 130/85$ mm Hg, or fasting glucose ≥ 110 mg/dL. Metabolic syndrome was diagnosed in the presence of 3 or more of these criteria.

Plasma concentrations of CRP were measured by means of particle-enhanced immunonephelometry with the Behring nephlometer method using N Latex CRP mono reagent (Behring Werke, Marburg, Germany). The assay

was linear from 0.175 to 230 mg/L; calibrators and controls (Rheumatology control CL-I) were supplied by the manufacturer (Behring Diagnostics, Westwood, MA) and were used for each batch of measurements.

Statistical Methods

Values are expressed as mean ± SD. All of the analyses were carried out using a statistical package (SPSS Inc, Chicago, IL, USA). The differences between the data of the 2 groups were compared by unpaired Student's t test. We used partial correlation coefficients to show the correlation between a metabolic syndrome components and CRP levels. Multivariate logistic regression analyses were used to test the association among metabolic syndrome components and CRP. Data are expressed as odds ratios and corresponding 95% confidence intervals. A value of $p < 0.05$ was accepted as statistically significant.

Results

There were no differences between the study groups in age and sex. Clinical characteristics of patients are shown in Table I.

The metabolic syndrome group included 24 men and 26 women with a mean age of 41.1 ±6.9 (29–62 years); the control group included 18 men and 22 women with a mean age of 41.3 ±6.7 (23–52 years). Systolic and diastolic blood pressure of metabolic syndrome group were found significantly higher than those of the control group (systolic 142.4 ±15.4 vs 125.2 ±13.3 mm Hg, $p < 0.01$ and diastolic 85.3 ±12.5 vs 76.3 ±10.2 mm Hg, $p < 0.01$, respectively). BMI of metabolic syndrome group was significantly higher than that of control group ($p < 0.001$). Central obesity was marked especially in women. Total cholesterol, triglyceride, and LDL-cholesterol levels were found significantly higher in the metabolic syndrome group ($p < 0.01$, $p < 0.001$, $p < 0.01$, respectively). HDL-cholesterol level was significantly lower in the metabolic syndrome group ($p < 0.001$). Laboratory values of patients are shown in Table II. Baseline CRP levels are shown in Table II. CRP levels were significantly higher in the metabolic syndrome group compared to levels in the control group (10.6 ±5.4 mg/L vs 3.5 ±0.8 mg/L, $p < 0.001$).

The distribution of high-sensitivity CRP values ranged from 3.4 to 24.8 mg/L in the metabolic syndrome group. Subjects with concentrations ≥ 10 mg/L comprised 45% of men and 55% of women, whereas only 8% of patients had val-

Table I. Main clinical characteristics of patients with metabolic syndrome and control group.

	Metabolic Syndrome (n=50)	Control Group (n=40)	p Value
Age (years)	41.1 ±6.9	41.3 ±6.7	>0.05
Male/Female	24/26	18/22	>0.05
Systolic BP (mm Hg)	142.4 ±15.4	125.2 ±13.3	<0.01
Diastolic BP (mm Hg)	85.3 ±12.5	76.3 ±10.2	<0.01
Waist circumference (cm)	105.7 ±8.6	76.3 ±8	<0.01
Waist to hip ratio	0.93 ±0.02	0.87 ±0.01	<0.01
Height (cm)	159.9 ±7.2	164.6 ±4.9	<0.01
Weight (kg)	93.1 ±9.5	66 ±5.7	<0.001
Body mass index (kg/m^2)	36.2 ±4.1	24 ±1.8	<0.001

BP = blood pressure.

Table II. Laboratory findings of patients.

	Metabolic Syndrome (n = 50)	Control Group (n = 40)	p Value
Glucose (mg/dL)	119.3 ± 10.4	87.5 ± 6.9	< 0.01
OGTT (mg/dL)	153.7 ± 9.8	94.2 ± 7.7	< 0.01
HDL-cholesterol (mg/dL)	42.9 ± 7	54.3 ± 8.9	< 0.01
LDL-cholesterol (mg/dL)	168.6 ± 17.6	108.1 ± 29.2	< 0.01
Total cholesterol (mg/dL)	256.3 ± 14.4	185.3 ± 29.4	< 0.01
Triglycerides (mg/dL)	243.7 ± 44.9	129.1 ± 43.1	< 0.01
CRP (mg/L)	10.6 ± 5.4	3.5 ± 0.8	< 0.01

HDL = high-density lipoprotein; CRP = C-reactive protein; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test.

ues ≥ 20 mg/L in the metabolic syndrome group. The distribution of high-sensitivity CRP values ranged from 2.3 to 6 mg/L in control group. Subjects with concentrations ≥ 5 mg/L comprised 7% of men and 7% of women, and CRP level exceeded 10 mg/L in none of the control group.

Table III shows the results of partial correlation analyses of factor relating to plasma CRP level. Plasma CRP also had significant correlation with BMI, waist circumference, waist-to-hip ratio, fasting plasma glucose, blood pressure, and total cholesterol in the metabolic syndrome group. Despite strong correlation between total cholesterol ($p < 0.001$) and CRP, there was a weak correlation between LDL-cholesterol ($p = 0.033$) and CRP. HDL-cholesterol did not significantly correlate with CRP ($p > 0.05$).

The results of logistics regression analysis are shown in Table IV. In the multiple regression analysis, BMI ($p < 0.01$), waist circumference ($p < 0.01$), and fasting plasma glucose ($p < 0.01$) remained as factors showing independent correlation with plasma CRP.

Discussion

In 1930, Tillet and Francis described an acute phase reactant in the serum of patients with pneumonia that they called C-reactive protein because of its precipitation with pneumococcal C-polysaccharide.[20] Smoking, obesity, and aging are also associated with increased levels of CRP.[21] Increases in CRP concentration have been associated with increased cardiovascular events in asymptomatic, but high-risk subjects. Patients with metabolic syndrome carry a high risk for coronary artery disease even if they are asymptomatic.

Findings from the Honolulu Heart Program indicate that CRP, as a marker of inflammation, is associated with coronary events that can occur up to 15 years from the time when CRP is first determined.[22] Although data from the Honolulu Heart Program provide further evidence of an inflammatory component in cardiovascular disease, it remains uncertain how this component contributes to the pathophysiology of atherosclerotic processes. Associations could be through the general processes of cellular proliferation, lipid accumulation, thrombus formation, or all three. Levels of CRP may also have direct effects on complement activation, tissue factor expression, or endothelial cell activation.[23,24] In addition, elevations in CRP concentrations could be in response to the presence of infectious agents that may have associations with atherosclerosis.[5] It may also be that CRP is associated with cardiovascular disease risk throughout life, although it may possibly reflect different stages in its pathophysiology.[25]

CRP and activated complement are found in atherosclerotic plaques. Some support for the hypothesis that CRP is pro-atherogenic is evidence

Table III. Partial correlation coefficient (r) and p value between CRP and various risk parameters in patients with metabolic syndrome.

	r	p Value
Systolic BP (mm Hg)	0.143	0.023
Diastolic BP (mm Hg)	0.095	0.035
Waist circumference (cm)	0.633	< 0.001
Waist-to-hip ratio	0.232	< 0.01
Body mass index (kg/m^2)	0.758	< 0.001
Glucose (mg/dL)	0.247	0.043
OGTT (mg/dL)	0.328	0.153
HDL-cholesterol (mg/dL)	–0.346	0.148
LDL-cholesterol (mg/dL)	0.353	0.033
Total cholesterol (mg/dL)	0.783	< 0.001
Triglycerides (mg/dL)	0.423	0.033

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test.

Table IV. Multivariate logistic regression analysis in patients with metabolic syndrome.

	Odds Ratio	95% Confidence Interval	p Value
Age (years)	0.78	0.19–3.07	0.72
BMI (kg/m^2)	6.34	1.38–29.08	< 0.01
Waist circumference (cm)	4.21	1.12–6.12	< 0.01
Glucose (mg/dL)	19.42	1.82–206.56	< 0.01
HDL-cholesterol (mg/dL)	0.89	0.82–1.98	0.22
Triglycerides (mg/dL)	1.12	0.81–2.98	0.32

BMI = body-mass index; HDL = high-density lipoprotein.

that CRP binds to LDL and promotes its uptake by macrophages via the CD32 receptor.[26-28] CRP may mediate tissue damage through activation of the complement system by binding to modified LDL with exposed phosphorylcholine.[29] Activated complement, enzymatically modified LDL and CRP can be found in proximity to each other in the deep intima of early atherosclerotic coronary artery lesions. Uptake of enzymatically modified LDL by macrophages also releases IL-6 thus providing a potential forward feedback loop to increase liver production of CRP and enhance local

complement activation.[30] Endothelial cell adhesion molecule expression can be 10-fold by 10 mg/L CRP in the presence of serum.[23] CRP also stimulates peripheral monocytes to produce tissue factor, a potent stimulus for thrombosis.[24] In patients with metabolic syndrome, LDL-cholesterol and triglyceride levels were high while HDL-cholesterol level was low. This lipid profile is especially important for the development of atherosclerosis. Increased CRP levels may play on additional role in the disease process.

Although LDL-cholesterol was an independent risk factor for atherosclerosis, a weak correlation with CRP levels was found in our study. Similar to our study, a weak correlation between the CRP levels and LDL-cholesterol was found in Quebec Cardiovascular Study.[31]

Another important point is increased BMI in patients with metabolic syndrome. CRP is also elevated in obesity. BMI and CRP have been correlated in young adults, middle-aged men, and elderly men and women from the Cardiovascular Health Study.[32] Plasma tumor necrosis factor–α (TNF-α) and IL-6 are produced by adipocytes and are elevated in obese subjects.[33,34] TNF-α also induces IL-6 production, which in turn regulates the production of CRP in liver.[35] Therefore, as TNF-α and IL-6 production is reduced by weight loss, one would expect CRP to be reduced as well. Weight loss decreases both CRP levels and cardiovascular risk in metabolic syndrome. It was seen that weight loss decreased CRP levels by 26% in healthy obese women.[36] CRP changes were correlated with changes in body weight and fat mass. In our study, there was a positive correlation between BMI and CRP. In our multivariate analyses, there was an independent relationship between BMI and CRP levels. This result was similar to that of previous studies and points out that obesity itself increased the CRP levels free from metabolic syndrome. However, central obesity is seen commonly in patients with metabolic syndrome. In the previous study, waist circumference has been shown to be the best antropometric index to predict visceral abdominal tissue accumulation.[37,38] In our study, central obesity was the predominant type of obesity in the patients and we found that CRP levels increased parallel to the waist circumference. Similar to our study; CRP is associated with waist circumference in some studies,[39-41] and this association often persists after adjustment for BMI.[42] This indication that increased CRP levels in patients with metabolic syndrome compared to normal subjects is not simply dependent on the increased BMI and that the main problem is the abdominal obesity seen in the patients with metabolic syndrome.

Our study has several limitations. We did not document coronary artery disease by coronary angiography and investigate the CRP levels in patients with and without coronary artery disease. But the patients and the control group were completely asymptomatic and had electrocardiogram free of ischemic changes. Our main aim was to investigate CRP levels in asymptomatic patients or in patients without overt coronary artery disease.

Conclusion

In conclusion, in patients with metabolic syndrome, CRP levels in the presently accepted upper normal range or higher are accompanied by an increased long-term risk for development of cardiovascular events. CRP is a moderately good predictor of acute vascular events. The high-sensitivity assay for exact determination of relatively low CRP levels is reliable, can be carried out easily, and might, therefore, represent a new and noninvasive tool to help to identify an increased risk for future coronary events in patients with metabolic syndrome. Intervention, which reduces CRP, may be effective in preventing the occurrence of cardiovascular events. Obesity and insulin resistance are associated with elevated CRP and caloric restriction and weight loss decreases CRP and possibly may damp down inflammation and reduce acute events.

REFERENCES

1. Tracy RP, Lemaitre RN, Psaty BM, et al: Relationship of C-reactive protein to risk of cardiovascular disease in the elderly: Results from the Cardiovascular Health Study and the Rural Promotion Project. Arterioscler Thromb Vasc Biol 17:1121-1127, 1997.
2. Berliner JA, Navb M, Fogelman AM, et al: Atherosclerosis: Basic mechanisms, oxidation, inflammation, and genetics. Circulation 91:2488-2496, 1995.
3. Liuzzo G, Biasucci LM, Gallimore JR, et al: The prognostic value of C-reactive protein and serum amyloid protein in severe unstable angina. N Engl J Med 331:417-424, 1994.
4. Ridker PM, Cushman M, Stampfer MJ, et al: Inflammation, aspirin, and the risk of cardiovascular dis-

ease in apparently healthy men. N Engl J Med 336: 973-979, 1997.

5. Fagerberg B, Gnarpe J, Gnarpe H, et al: Chlamydia pneumoniae but not cytomegalovirus antibodies are associated with future risk of stroke and cardiovascular disease: A prospective study in middle-aged to elderly men with treated hypertension. Stroke 30:299-305, 1999.
6. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group; Haverkate F, Thompson SG, Pyke SD, et al: Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 349(9050):462-466, 1997.
7. Ridker PM, Glynn RJ, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 97:2007-2011, 1998.
8. Ridker PM, Hennekens CH, Buring JE, et al: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 342:836-843, 2000.
9. Danesh J, Whincup P, Walker M, et al: Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. BMJ 321:199-204, 2000.
10. Steel DM, Whitehead AS: The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. Immunol Today 15:81-88, 1994.
11. Weinhold B, Ruther U: Interleukin-6-dependent and independent regulation of human C-reactive protein gene. Biochem J 327:425-429, 1997.
12. Heilbronn LK, Clifton PM: C-reactive protein and coronary artery disease: Influence of obesity, caloric restriction and weight loss. J Nutr Biochem 13:316-321, 2002.
13. Haffner SM, Valdez RA, Hazuda HP, et al: Prospective analysis of the resistance syndrome (syndrome X). Diabetes 41:715-722, 1992.
14. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988.
15. Kaplan NM: The deadly quartet: Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 149:1514-1520, 1989.
16. Yudkin JS: Relationship of serum C3 complement with insulin resistance and coronary heart disease-cause, consequence or common antecedent? Eur Heart J 21:1036-1039, 2000.
17. Ross R: Atherosclerosis an inflammatory disease. N Engl J Med 340:115-126, 1999.
18. Danesh J, Collins R, Appleby P, et al: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: Meta-analyses of prospective studies. JAMA 279:1477-1482, 1998.
19. Expert Panel on Detection, evaluation, and treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285:2486-2497, 2001.
20. Tillett WS, Francis T: Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med 52:561-567, 1930.
21. Koenig W, Sund M, Frohlich M, et al: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. Results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 99:237-242, 1999.
22. Knutsen R, Knutsen SF, Curb JD, et al: The incidence of coronary heart disease in the Honolulu Heart Program. J Clin Epidemiol 41:293-243, 1988.
23. Pasceri V, Willerson JT, Yeh ET: Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 102:2165-2168, 2000.
24. Cermak J, Key N, Bach R, et al: C-reactive protein induces human peripheral blood monocytes to tissue factor. Blood 82:513-520, 1993.
25. Tracy RP: Inflammation markers and coronary heart disease. Cur Opin Lipidol 10:435-441, 1999.
26. Reynolds GD, Vance RP: C-reactive protein immunohistochemical localization in normal and atherosclerotic human aortas. Arch Pathol Lab Med 111:265-269, 1987.
27. Vlaicu R, Niculescu F, Rus HG, et al: Immunohistochemical localization of terminal C5b-9 complement complex in human aortic fibrous plaque. Atherosclerosis 57:163-177, 1985.
28. Zwaka TP, Hombach V, Torzewski J: C-reactive protein-mediated low density lipoprotein uptake by macrophages: Implications for atherosclerosis. Circulation 103:1194-1197, 2001.
29. Bhakdi S, Torzewski M, Klouche M, et al: Complement and atherogenesis: Binding of CRP to degraded, nonoxidized LDL enhances complement activation. Arterioscler Thromb Vasc Biol 19:2348-2354, 1999.
30. Klouche M, Gottschling S, Gerl V, et al: Atherogenic properties of enzymatically degraded LDL: Selective induction of MCP-1 and cytotoxic effects on human macrophages. Arterioscler Thromb Biol Vasc 18: 1376-1385, 1998.
31. St-Pierre AC, Bergeron J, Pirro M, et al: Effect of plasma C-reactive protein levels in modulating the risk of coronary heart disease associated with small, dense, low-density lipoproteins in men (The Quebec Cardiovascular Study). Am J Cardiol 91:55-58, 2003.
32. Tracy RP, Lemaitre RN, Psaty BM, et al: Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and Rural Health Promotion Project. Arterioscler Thromb Vasc Biol 17:1121-1127, 1997.
33. Hotamisligil GS, Arner P, Caro JF, et al: Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 95:2409-2415, 1995.
34. Bastard JP, Jardel C, Bruckert E, et al: Elevated lev-

els of interleukin-6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab 85:3338-3342, 2000.

35. Amrani Y, Ammit AJ, Panettieri RA: Tumor necrosis factor receptor (TNFR) 1, but not TNFR2, mediates tumor necrosis factor–alpha-induced interleukin-6 and RANTES in human airway smooth muscle cells: Role of p38 and p42/44 mitogen-activated protein kinases. Mol Pharmacol 60:646-655, 2001.
36. Heilbornn LK, Noakes M, Clifton PM: Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. Arterioscler Thromb Vasc Biol 21:968-970, 2001.
37. Pouliot MC, Despres JP, Lemieux S, et al: Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 73:460-468, 1994.
38. Lemieux S, Prud'homme D, Bouchard C, et al: A single threshold value of waist girth identifies normal-weight and over-weight subjects with excess visceral adipose tissue. Am J Clin Nutr 64:685-693, 1996.
39. Hak AE, Stehouwer CDA, Bots ML, et al: Associations of C-reactive protein with measures of obesity, insulin resistance and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol 19:1986-1991, 1999.
40. Festa A, D'Agostino R, Howard G, et al: Chronic subclinical inflammation as part of the insulin resistance syndrome. The insulin resistance atherosclerosis study (IRAS). Circulation 102:42-47, 2000.
41. Yudkin JS, Stehouwer CD, Emeis JJ, et al: C-reactive protein in healthy subjects, Associations with obesity, insulin resistance, and endothelial dysfunction. A potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 19:972-978, 1999.
42. Visser M, Bouter LM, McQuillan GM, et al: Elevated C-reactive protein in overweight and obese adults. JAMA 282:2131-2135, 1999.