Clinical Usefulness of High-Sensitivity C-Reactive Protein in Predicting Risk of the Metabolic Syndrome: Epidemiologic Evidence

Yiqing Song, MD, ScD

[N A J Med Sci. 2008;1(1):36-37.]

C-reactive protein (CRP) is an acute-phase protein, which is primarily synthesized in the liver. In response to most forms of inflammation, infection, and tissue damage, plasma levels of CRP in human body may rise rapidly and markedly, as much as 100 or 1000-fold or more during the acute phase. In epidemiological studies, CRP levels well below the conventional clinical upper limit of 10 mg/L (as measured by high sensitivity CRP) have consistently been predictive of cardiovascular disease[1,2] and type 2 diabetes in various populations.[3] The "high sensitivity" refers to the lower detection limit of the assay procedures being used than previous commercial assays routinely used for clinical measurements.[4] Highly sensitive assays for CRP are widely used in epidemiologic studies to precisely measure values within the range less than 10 mg/L. High-sensitivity CRP thus has become a clinically useful marker of low-grade chronic inflammation. Low-grade chronic inflammation may be one of the common antecedents underlying the clustering of obesity, impaired glucose tolerance, dyslipidemia, and hypertension, known as the metabolic syndrome. Ranges of <1, 1 to 3, and >3 mg/L, which correspond to approximate tertiles of the CRP distribution in healthy US adults, are used to denote low-, moderate-, and high-risk cardiovascular groups. Of note, CVD and type 2 diabetes are the major sequelae of the metabolic syndrome. CRP independently predicts both CVD and type 2 diabetes, but it is unknown whether CRP evaluation is a valuable addition to the metabolic syndrome for risk assessment of CVD and diabetes.

As a reliable marker of systemic inflammation, CRP levels have been observed to be associated with all features of the metabolic syndrome including abdominal obesity, hypertension, hyperglycemia and/or hyperinsulinemia, and dyslipidemia (high triglyceride-low HDL cholesterol). Regardless of diverse definitions used for the metabolic syndrome in different studies, there is an emerging consensus that CRP levels are also associated with the presence of metabolic syndrome itself as an entity. Earlier cross-sectional studies reported elevated levels of various inflammatory markers in diabetic patients with features of the metabolic syndrome. The findings were also supported by several cross-sectional studies in nondiabetic populations that utilized variable definitions of the metabolic syndrome (summarized in **Table 1**). These cross-sectional analyses clearly showed that elevated CRP levels correlate significantly with features of the metabolic syndrome using either strict NCEP-ATP III criteria or modified NCEP-based definitions. In addition, several cross-sectional studies had observed gender-specific association between CRP levels and the metabolic syndrome.[5] Such gender-based differences may indicate an underlying interrelationship between sex hormones and the proinflammatory response, although greater adiposity and larger sample size in women than men could, at least in part, explain such sex-differences.

Although prospective data are limited, the available evidence parallels the findings from cross-sectional studies, suggesting that low-grade chronic inflammation, as indicated by CRP levels, contributes to the development of metabolic syndrome.[6] Beyond the assessment of the metabolic syndrome, CRP has been shown to improve the clinical risk assessment to predict future risk of developing CVD and type 2 diabetes in prospective observational studies.[5, 7, 8]

Overall, epidemiologic data provide a clear message that addition of CRP as a criterion for the diagnosis of metabolic syndrome may add more prognostic information. Adding it formally to the metabolic syndrome definition could improve our ability to identify high-risk patients in both primary and secondary prevention. However, most studies have been cross-sectional and were unable to fully account for residual confounders, particularly obesity or insulin resistance, leaving unresolved the independent values of CRP measurement for predicting CVD and type 2 diabetes. There is a notable lack of data from prospective studies regarding the practical clinical and public health significance of incorporating CRP measurements into the metabolic syndrome definition. Although careful consideration should be given to the clinical value of adding CRP, more research in this area is needed. From a clinical perspective, physicians should continue to focus on evaluating and treating individuals based on traditional risk factors.

Yiqing Song, MD, ScD
Division of Preventive Medicine
Department of Medicine
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts 02215, USA
Tel: 617-278-0913 Fax: 617-731-3843
Email: ysong3@rics.bwh.harvard.edu

References

1. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA. 1998;279(18):1477-1482.

2. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342(12):836-843.
3. Liu S, Tinker L, Song Y, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. Arch Intern Med. 2007;167(15):1676-1685.
4. Ridker PM: High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001;103(13):1813-1818.
5. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Sr., Wilson PW: C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation. 2004;110(4):380-385.
6. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM: Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes Care. 2002;25(11):2016-2021.
7. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation. 2003;107(3):391-397.
8. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation. 2003;108(4):414-419.

Table 1. Available Epidemiologic studies showing the relationship between CRP and the metabolic syndrome

Study (Reference)	**Participants**	**Age (mean or range)**	**CRP levels in response to the number of metabolic components**
Festa et al, 2000	1088 US participants ((non-Hispanic whites, blacks, and Hispanic)	54.7	0→4, from 1.08 to 4.01 mg/L
Frohlich et al, 2000	1703 Germans (747 men and 956 women)	18-89	0→4, from 1.15 to 1.94 mg/L
Ridker et al, 2003	14719 US women (mostly Caucasian)	≥45	0→4, from 0.68 to 3.88 mg/L
Rutter et al, 2004	3037 Americans (1681 women and 1356 men)	26-82	0→4, from 2.2 to 6.6 mg/L
Florez et al, 2005	190 (83 men and 107 women) (96% Hispanics)	25-75	0→4, from 2.7 to 6.3 mg/L (women); 0→4, from 2.4 to 3.5 mg/L (men).
Lamonte et al, 2005	135 Americans (44 African, 45 Native, and 46 Caucasian)	55	0→4, from 1.6 to 4.7 mg/L
Lim et al, 2005	9773 Koreans (4611 men and 5162 women)	40-69	0→4, from 1.4 to 2.4 mg/L
Nakanishi et al, 2005	1715 Japanese (723 men and 992 women)	40-69	0→3, from 0.39 to 0.77 mg/L (non-obese men); 1→3, from 0.44 to 0.81 mg/L (obese men); 0→3, from 0.28 to 0.61 mg/L (non-obese women); 1→3, from 0.58 to 0.93 mg/L (obese women)
Santos et al, 2005	957 Portuguese (358 men and 599 women)	18-92	<3 vs. ≥3: 0.97mg/L vs. 3.18 mg/L.

The metabolic syndrome components included obesity defined by BMI or waist circumference; glucose intolerance; high blood pressure; dyslipidemia (low HDL and high triglycerides).