ISSN 1755-6783

Annals of Tropical Medicine and Public Health

www.atmph.org

Official Publication of
Africa Health Research Organization

Volume 5 | Issue 2 | Mar-Apr 2012

Wolters Kluwer Health | Medknow

ORIGINAL ARTICLE

Highly sensitive C reactive protein in patients with metabolic syndrome and cardiovascular disease

Mukta N. Chowta, Prabha M. Adhikari, Rishav Sinha, Sahana D. Acharya, Gopalakrishna HN, John T. Ramapuram

Department of Medicine and Pharmacology, Kasturba Medical College, Mangalore, Manipal University, India

ABSTRACT

Context: Although there are several studies reported in the western literature regarding the association of C reactive protein (CRP) level with components of metabolic syndrome, data in the Indian population were lacking. As there will be a considerable difference in the profile of risk factors for cardiovascular diseases (CVDs), studies regarding the correlation of CRP level with cardiovascular risk factors and metabolic syndrome in the Indian population are required. **Objective:** To correlate the highly sensitive CRP (hsCRP) level to individual components of metabolic syndrome and coronary vascular disease. **Materials and Methods**: Forty patients who were diagnosed clinically with metabolic syndrome were included in the study. Detailed history with regard to diabetes mellitus, hypertension and other CVD was collected from each patient. All the patients underwent complete physical examination, including ECG. Height, weight, fasting blood glucose and lipid levels were measured in all the patients. CVD was assessed with the following: new-onset angina, fatal and non-fatal myocardial infarction or stroke, transient ischemic attack, heart failure or intermittent claudication. **Results:** The mean hsCRP level was higher in patients with CVD compared with those without CVD. The CRP level correlation with CVD showed a statistically significant correlation. hsCRP level was very high in eight hypertensive patients, whereas it was very high in five normotensives. But, statistical analysis has not shown any significant correlation between hypertension and hsCRP level. Similarly, although a higher hsCRP level was seen in diabeteics, statistical analysis failed to show a significant correlation between diabetes and the hsCRP level. Analyses of hsCRP correlation with body mass index, fasting glucose, cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein did not show a significant correlation with the hsCRP level. **Conclusions:** Increased hsCRP levels are associated with an increase in the incidence of CVDs. Higher values of hsCRP were observed in patients with hypertension and diabetes. No correlation was seen between hsCRP and components of the metabolic syndrome.

Key words: Cardiovascular disease, hsCRP, Metabolic syndrome

Introduction

The metabolic syndrome, also termed as insulin-resistance syndrome, is the concurrence in an individual of multiple metabolic abnormalities associated with cardiovascular disease (CVD). It represents a global public health problem. Reaven's[1] first definition of the metabolic syndrome included these components: hyperglycemia, abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol concentration, and hypertension. Patients with metabolic syndrome are at an increased risk for diabetes and cardiovascular events. The ATP-III (adult treatment panel III) guideline suggests a working definition of the metabolic syndrome, which includes the presence of at least three of the following characteristics: hyperglycemia, abdominal obesity, hypertriglyceridemia, reduced HDL cholesterol, hypertension and high fasting glucose.[2]

Access this article online	
Quick Response Code:	Website: www.atmph.org
	DOI: 10.4103/1755-6783.95960

The term acute-phase response is used to describe the greatly increased synthesis and secretion of certain plasma proteins, including C reactive protein (CRP), principally by the liver, following trauma, tissue necrosis, infections and the acute effects of inflammatory diseases.[3] Inflammation releases cytokines, and the cytokine Interlukin-6 is thought to be largely responsible for triggering the production

Correspondence:

Dr. Prabha M. Adhikari, Department of Medicine and Pharmacology, Kasturba Medical College, Manipal University, Mangalore - 575 001, India.

E-mail: muktachowta@yahoo.co.in

of CRP, which is thus generally viewed as a marker of inflammation, with very high values associated with acute inflammation. CRP belongs to the pentraxin family of proteins. This protein is very sensitive to inflammation, and its concentration can increase rapidly in response to a wide range of stimuli. Originally described in 1930, CRP measurements served mostly in a diagnostic, although a non-specific one, and in a monitoring role in such fields as infectious diseases and rheumatology. In the past decade, as the role of inflammation in CVD became appreciated, interest turned to CRP as a possible risk marker for CVD. Since then, studies have shown that the CRP concentration is positively associated with CVD incidence and mortality, even when the concentration is <3.0 mg/L, which was previously thought to be "normal." CRP has proven to be a strong, independent predictor of both incidence of diabetes and incidence of CVD. CRP levels correlate with several components of the metabolic syndrome, including fasting insulin, microalbuminuria and impaired fibrinolysis, which are not easily evaluated in usual clinical practice.[4]

Although there are several studies reported in the western literature regarding the association of CRP level with components of metabolic syndrome, data in the Indian population was lacking. As there will be considerable difference in the profile of risk factors for CVDs, studies regarding the correlation of CRP level with cardiovascular risk factors and metabolic syndrome in the Indian population are required. Hence, this study was undertaken with the objective of measuring the highly sensitive CRP (hsCRP) level in patients with a diagnosis of metabolic syndrome and to correlate the hsCRP level to individual components of the metabolic syndrome. The study was also intended to correlate the level of hsCRP with coronary vascular disease

Materials and Methods

The subjects were participants in a clinical trial on hypolipidemic drug in patients with metabolic syndrome. The study has been approved by the institutional ethics committee and written informed consent was taken from each patient who participated in the study. Forty patients who were diagnosed clinically with metabolic syndrome as per IDF 2005 criteria[5] were included in the study. Detailed history with regard to diabetes mellitus, hypertension and other CVD was collected from each patient. Concomitant medications taken by the patients were also noted. All the patients underwent complete physical examination, including ECG. Height, weight, fasting blood glucose and lipid levels were measured in all the patients. CVD was assessed with the following: new-onset angina, fatal and non-fatal myocardial infarction or stroke, transient ischemic attack, heart failure or intermittent claudication. Body mass index (BMI) was calculated and patients with BMI less than 25 kg/m^2 were considered as normal, whereas those with BMI more than 25 kg/m^2 were considered overweight.

hsCRP level was measured by using a CRP test kit manufactured by Omega Diagnostics Ltd, Omega house, Hillfoots Business Village, Alva, FK12 5DQ, Scotland, United Kingdom, Scotland, United Kingdom, which utilizes the latex agglutination technique. hsCRP level less than 1 mg/L was considered as normal, more than 1 mg/L but less than 5mg/L was considered as high whereas a level more than 5 mg/L was considered as very high.

Descriptive statistics were generated for all study variables, including mean and SD for continuous variables and relative frequencies for categorical variables. The CRP level was correlated with the components of metabolic syndrome and the occurrence of cardiovascular disorders. Sample means between group with CVD and without CVD were compared using the Mann-Whitney U test. Spearmann's correlation coefficient was used to correlate hsCRP levels to BMI, fasting glucose, lipid profile, cholesterol and triglycerides.

Results

A total of 40 patients with the clinical diagnosis of metabolic syndrome were included in the study. Among them, seven were male and 33 were female. The mean age of the study population was 68 ± 9.41 years. Clinical and biochemical characteristics of the patients are shown in Table 1. Among the 40 patients, 10 were on antihypertensives, nine were on both antihypertensives and antidiabetics, seven were on only antidiabetics and four patients were also taking aspirin.

Of the 40 patients, 13 had CVD. Among these 13 patients, one patient had normal hsCRP, five had high hsCRP and seven patients had very high hsCRP level. The remaining patients were without CVD. Among these patients, four had normal hsCRP, 17 had high hsCRP and six patients had very high hsCRP [Table 2]. The mean CRP level was higher in patients with CVD (6.35 mg/L) compared with that in those without CVD (3.83 mg/L). hsCRP level correlation with CVD was performed by using the Mann-Whitney U test, which showed a statistically significant correlation (P = 0.048) [Table 2].

Table 1: Clinical and biochemical characteristics

Variables	Mean ± SD (*n* = 40)
Age (years)	67.82 ± 9.41
BMI (kg/m^2)	23.53 ± 4.23
Fasting glucose (mg/dl)	116.80 ± 49.45
Cholesterol (mg/dl)	237.77 ± 49.55
Triglycerides (mg/dl)	164.20 ± 84.25
HDL cholesterol (mg/dl)	46.43 ± 15.89
LDL cholesterol (mg/dl)	153.82 ± 34.63
hsCRP (mg/L)	4.65 ± 3.97

Table 2: hsCRP level in relation to CVD, hypertension and diabetes mellitus

hsCRP level	CVD, n (%)		Hypertension, n (%)		Diabetes mellitus, n (%)	
	Present	Absent	Present	Absent	Present	Absent
Normal (<1 mg/L)	1 (20)	4 (80)	4	2	2	4
High (1–5mg/L)	5 (23)	17 (77)	11	10	10	11
Very high (>5 mg/L)	7 (54)	6 (46)	8	5	6	7
Mean CRP (mg/L)	6.35*	3.83	4.75	4.51	4.74	4.58

*P = 0.048, significant Mann-Whitney U test

Table 3: Correlation of hsCRP with components of metabolic syndrome

Variables (*n* = 40)	Coefficient	*P*-value
BMI	-0.105	0.519
Fasting glucose	-0.089	0.585
Cholesterol	-0.28	0.08
Triglycerides	-0.096	0.558
HDL cholesterol	-0.147	0.371
LDL cholesterol	-0.277	0.083

(Spearmann correlation coefficient)

In the present study, 23 had hypertension and the remaining were normotensives. Mean hsCRP in hypertensives was 4.75 mg/L, whereas in normotensives the mean hsCRP was lesser (4.51 mg/L). But, statistical analysis has not shown any significant correlation between hypertension and hsCRP level (Mann-Whitney U test, P = 0.603, Table 2). hsCRP level was very high in eight hypertensive patients, whereas it was very high in five normotensives.

The present study involved 18 patients with type 2 diabetes mellitus, and the remaining 22 were non-diabetics. The mean hsCRP level was higher in diabetics (4.74 mg/L) compared with non-diabetics (4.58 mg/L). But, the statistical analysis failed to show a significant correlation (P = 0.394) [Table 3].

Among the 40 patients, 27 had BMI less than 25 kg/m^2, whereas 13 had BMI more than 25kg/m^2 (overweight). The mean hsCRP in patients was lesser in patients of normal BMI (3.73 mg/L) compared with overweight patients (4.46 mg/L). But, the statistical difference was not significant (P = 0.4). The mean hsCRP level in males was higher (7.04 mg/L) compared with that in females (4.14 mg/L). But, it was statistically not significant (P = 972).

Table 3 shows the analyses of hsCRP correlation with BMI, fasting glucose, cholesterol, triglycerides, HDL and LDL (Spearmann correlation coefficient). None of these components have shown a significant correlation with the hsCRP levels.

Discussion

Associations between inflammation, metabolic syndrome and CVD have been reported. A clinical marker of inflammation is high-sensitivity CRP,[6] an acute-phase reactant that is produced by the liver in response to pro-inflammatory cytokines, such as interleukin-6, and reflects low-grade systemic inflammation. Inflammation releases cytokines, and the cytokine Interlukin-6 is thought to be largely responsible for triggering the production of CRP, which is thus generally viewed as a marker of inflammation, with very high values associated with acute inflammation. Chronic, low-level inflammation can result in near-normal, but nevertheless elevated, values. Elevated levels of hs-CRP have been shown to be predictive of increased risk of coronary artery disease in apparently healthy men and women. We investigated the association of metabolic syndrome components (hypertension, obesity, elevated triglyceride concentrations, decreased HDL-cholesterol concentrations and elevated fasting glucose) and CVD with hsCRP concentrations.[6]

Our study has shown a positive correlation between hsCRP level and CVD occurrence. Of 13 patients who had CVD, 12 had elevated levels of hsCRP. There are a number of other studies reported in the western literature[4,6] that showed a positive correlation between CRP levels and CVD. Ridker[7] has reviewed nine studies published between 1996 and 2000. Findings of these studies as well as our study point toward the significance of determining the CRP level in diagnosing and predicting various cardiovascular pathologies.

However, the present study failed to show any

correlation between hsCRP level and the components of metabolic syndrome. This is in contrast to several studies that have shown a significant association between CRP level and parameters of metabolic syndrome.[8-10] Similar to our results, the study carried out by Vikram *et al.* also showed a lack of correlation of CRP level with fasting glucose and lipid profile.[11] Absence of positive correlation may be also due to concomitant medications like aspirin and antidiabetic agents taken by the patients. Aspirin and statins are known to reduce vascular inflammation, which may result in reduced levels of CRP in those patients who were on these medications.[12] A recent report suggests that PPAR-γ inhibitor like rosiglitazone directly reduces the CRP levels.[13]

The cross-sectional relations of CRP and features of the metabolic syndrome in other studies suggest that inflammation is strongly associated with insulin resistance and metabolic syndrome,[14] and it supports the hypothesis that inflammation plays an important role in the pathogenesis of diabetes and atherosclerosis. An important link between these conditions and obesity could be the pro-inflammatory cytokines produced by adipose tissue, such as tumor necrosis factor-α and Interleukin-6. These cytokines can influence insulin resistance and glucose uptake, promote hepatic fatty acid synthesis and increase hepatic CRP production. A central role for obesity in the pathogenesis of insulin resistance could explain why some studies have shown that the relationship between inflammatory markers and the risk of developing diabetes is attenuated after correction for obesity. Individual features of the metabolic syndrome, such as hypertension and dyslipidemia, could directly cause endothelial dysfunction and subclinical atherosclerosis, leading to inflammation and raised CRP. Alternatively, insulin resistance could increase hepatic CRP production by blocking insulin-mediated inhibition of acute-phase protein gene expression.[15,16]

Our study did not show a significant difference in hsCRP levels in males and females. The CRP level was higher in males than in females. The Mexico City Diabetes Study has shown that CRP levels were more strongly related to insulin resistance and features of the metabolic syndrome in women.[17] That study also showed that CRP levels predicted the development of metabolic syndrome and diabetes in women but not in men. Two more recent reports have shown that in a cross-sectional analysis, markers of inflammation, including CRP, were more strongly related to insulin resistance in women than in men.[18,19] Endogenous estrogen may be responsible for the gender difference. Also, women might have greater quantities of total body adipose tissue compared with men, and this could be the source of the pro-inflammatory cytokines. Han and coworkers[17] have suggested that inflammation might have a greater effect on insulin resistance in women than in men. Laboratory studies have shown that the pro-inflammatory cytokine Interleukin-6 can influence estradiol production by granulosa cells and therefore that chronic inflammation could theoretically mitigate the protective effect of estrogen on insulin resistance and body fat distribution.[20]

Rifai and Ridker suggest[21] that, in clinical practice, CRP evaluations should be avoided if there has been recent infection or trauma. They suggest that 2 weeks is sufficient for a return to basal values. CRP values greater than 15 gm/L indicate active or perhaps transient inflammation, and it was suggested that two CRP measurements a month apart provide a better picture, especially if a CRP value greater than 5 is obtained on the first determination. The implication of the guidelines is that the clinical assessment requires a more or less stable value, be it 0.1 or 10 mg/L, i.e. it is desirable to avoid clinical decisions based on an abnormally high value that is transitory.

Limitations of the present study must be considered, which include: use of selected cohorts derived from clinical trials, cross-sectional design, absent data about insulin resistance and glucose tolerance. The sample size was small and also there were difference in the criteria for inclusion of subjects in the study when compared with various other studies reported in the literature. Also, the group we studied was not homogenous; females were predominant. In the subgroup analysis, the number of patients was very less. All these factors would have affected the findings of our study.

To conclude, increased hsCRP levels are associated with an increase in the incidence of CVDs. Determining hsCRP levels in patients could add to the diagnostic and prognostic information for the patient in the context of cardiovascular disorders. Higher values of hsCRP were observed in patients with hypertension and diabetes. No correlation was seen between hsCRP and components of metabolic syndrome. Further research with a prospective longitudinal design in a larger sample may be needed to draw definite conclusions.

References

1. Reaven G. Metabolic syndrome. Pathophysiology and implications for management of cardiovascular disease. Circulation 2002;106:286-8.
2. 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 2001;285;2486-97.
3. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, *et al*. Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. BMJ 2000;321: 199-204.
4. Ford ES, Giles WH, Myers GL, Mannino DM. Population Distribution of High- Sensitivity C-reactive Protein among US Men: Findings from National Health and Nutrition Examination Survey 1999-2000. Clin Chem 2003;49:686-90.
5. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome. Available from: http://www.idf.org/. [Last accessed on 2005].
6. Chapidze G, Dolidze N, Enquobahrie DA, Kapanadze S, Latsabidze N, Williams MA. Metabolic syndrome and C-reactive protein among cardiology patients. Arch Med Res 2007;38:783-8.
7. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103:1813-8.
8. Malik S, Wong ND, Franklin S, Pio J, Fairchild C, Chen R. Cardiovascular disease in U.S. patients with metabolic syndrome, diabetes and elevated c-reactive protein. Diabetes Care 2005;28: 690-3.
9. 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 14719 initially healthy American women. Circulation 2003;107:391-7.
10. Florez H, Castillo-Florez S, Mendez A, Casanova-Romero P, Larreal-Urdaneta C, Lee D, et *al*. C-reactive protein is elevated in obese patients with the metabolic syndrome. Diabetes Res Clin Pract 2006;71:92-100.
11. Vikram NK, Misra A, Pandey RM, Dwivedi M, Luthra K, Dhingra V, *et al*. Association between subclinical inflammation and fasting insulin in urban young adult north Indian males. Indian J Med Res 2006;124:677-82.
12. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, *et al*. Inflammation, pravastatin and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation 1998;98:839-44.
13. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002;106:679-84.
14. Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42-7.
15. Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: Findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 2003;168:351-8.
16. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, *et al*. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671-4.
17. 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;25:2016-21.
18. Onat A, Ceyhan K, Başar O, Erer B, Toprak S, Sansoy V. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels: A prospective and cross-sectional evaluation. Atherosclerosis 2002;165:285-92.
19. Hak AE, Pols HA, Stehouwer CD, Meijer J, Kiliaan AJ, Hofman A, *et al*. Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: The Rotterdam study. J Clin Endocrinol Metab 2001;86:4398-405.
20. Alpizar E, Spicer LJ. Effects of interleukin-6 on proliferation and follicle-stimulating hormone-induced estradiol production by bovine granulosa cells *in vitro*: Dependence on size of follicle. Biol Reprod 1994;50:38-43.
21. Rifai N, Ridker PM. Proposed cardiovascular risk assessment algorithm using high-sensitivity C-reactive protein and lipid screening. Clin Chem 2001;47:28-30.

Cite this article as: Chowta MN, Adhikari PM, Sinha R, Acharya SD, Gopalakrishna HN, Ramapuram JT. Highly sensitive C reactive protein in patients with metabolic syndrome and cardiovascular disease. Ann Trop Med Public Health 2012;5:98-102.

Source of Support: Nil, **Conflict of Interest:** None declared.