



ISSN: 0975-833X

RESEARCH ARTICLE

A STUDY ON CLINICAL PROFILE OF METABOLIC SYNDROME IN ELDERLY AND ITS RELATION WITH HIGHLY SENSITIVE C-REACTIVE PROTEIN (hs CRP)

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ARTICLE INFO

Article History:

Received 09th February, 2017

Received in revised form

15th March, 2017

Accepted 20th April, 2017

Published online 23rd May, 2017

Key words:

MS-Metabolic Syndrome,
hs-CRP--highly sensitive
C-reactive protein.

ABSTRACT

Background: Highly sensitive C-reactive protein as a marker of systemic inflammation and the contribution of individual components of metabolic syndrome to elevated C- reactive protein was studied in the present study.

Objectives: To study the prevalence of various components of Metabolic Syndrome in elderly patients. Association of individual components of metabolic Syndrome with highly sensitive C-reactive protein.

Methods: Elderly subjects who were aged 60 years or more attending the hospital and satisfying at least 3 of the 5 components of metabolic syndrome according to the revised NCEP ATP III criteria of metabolic syndrome were included in the study. All the patients underwent detailed history and physical examination. Anthropometric data like height, weight, waist circumference were collected, BMI calculated with Quetelet index formula. The quantitative determination of hs CRP was done by immunoturbidometric assay by MODULAR P automated analyzers (Roche).

Results: Among 100 elderly patients Hypertension was prevalent in 93% , elevated Waist circumference 84% ,Diabetes Mellitus 81%, low HDL cholesterol or using lipid lowering drugs in 81% and elevated triglycerides or h/o using lipid lowering drugs in 75% of the study group. Highly Sensitive C- reactive protein was elevated in 60% of the study group. Hs CRP was more elevated in those patients with Hypertension and elevated Waist circumference than the other components of metabolic syndrome. Higher the number of the risk factors in a individual patient higher the elevation of hs-CRP.

Conclusions: Our study concluded that among all components of Metabolic syndrome, Hypertension and visceral adiposity were observed more frequently than the occurrence of other components in this elderly cohort of South India. Elevated waist circumference and hypertension were most commonly associated with systemic inflammation as measured by elevated hs CRP.

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Citation: Ramakrishna Janapati et al. 2017. "A study on clinical profile of metabolic syndrome in elderly and its relation with highly sensitive c-reactive protein (hs CRP)", *International Journal of Current Research*, 9, (05), 50663-50667.

INTRODUCTION

Metabolic syndrome (MS) was a widely prevalent and multi-factorial disorder with a rising prevalence worldwide, especially in developing nations. The syndrome had been given several names, including metabolic syndrome, insulin resistance syndrome, the plurimetabolic syndrome, and the deadly quartet, Reaven syndrome and syndrome X (Isomaa *et al.*, 2001). Metabolic syndrome (MS) was a very common clinical condition characterized by the clustering of cardiovascular risk factors related to insulin-resistance, including central obesity, impaired glucose tolerance, hypertension, and dyslipidemia (Giovanni Zuliani *et al.*, 2009). The Indian subcontinent is undergoing rapid epidemiological transition as non-communicable diseases like coronary heart

disease and type 2 diabetes mellitus are fast replacing infections as the leading cause of morbidity and mortality. The clinical relevance of the metabolic syndrome was related to its role in the development of cardiovascular disease. The need to do a study of this particular syndrome has arises in view of its ever increasing incidence in the last few decades due to rapid urbanization and sedentary life styles especially in younger population in the third world countries. There was also a increasing number of geriatric population of India due to increased life expectancy of developing nations. Inflammation was recognized as one of the central features of atherosclerosis and plays a key role in plaque rupture and therefore in most episodes of acute coronary events (Giovanni Zuliani *et al.*, 2009). The acute phase reactant C-reactive protein (CRP) was an extremely sensitive marker of systemic inflammation. CRP was widely used to evidence and estimate the severity of acute inflammation. Metabolic syndrome was also considered a proinflammatory state, and measurement of inflammatory

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markers like high-sensitivity C-reactive protein (hs-CRP) might improve the prediction of cardiovascular disease in patients with metabolic syndrome. Low grade systemic inflammation associated with moderate increase in CRP was now recognized as a strong and independent predictor of cardiovascular risk in middle aged subjects, and may be an important feature of the MS and development of type 2 diabetes (Ridker *et al.*, 2003; Rutter *et al.*, 2004). Several studies have demonstrated relationships between CRP and individual components of the MS. More recently MS was reported to be associated with increased CRP levels in older adults (Strandberg *et al.*, 2000; Chenillot *et al.*, 2000; Cankurtaran *et al.*, 2006). Increased abdominal fat mass was found to be independently associated with the MS in men and women also at an advanced age of 70-79 years (Scuteri *et al.*, 2005; Myoung-Hee *et al.*, 2004). India has the distinction of having the highest number of T2 Diabetics individuals worldwide. India has and will continue to have the highest number of elderly patients with metabolic syndrome in the world. Furthermore, Asian Indians are known to be at a high risk for T2D, CVD, and metabolic syndrome (Anubha Mahajan *et al.*, 2009). The present study aimed to determine the prevalence of various components of metabolic syndrome and their correlation with highly sensitive C-reactive protein (hs CRP), a novel marker of systemic low grade inflammation in elderly population attending a tertiary care hospital in the state of Telangana, south India.

MATERIALS AND METHODS

This study was an observational cross sectional study on elderly population attending a tertiary care hospital for regular check up. Participants were included into the study if they are aged 60 years or more and satisfying at least three of the criteria of metabolic syndrome. Metabolic syndrome was defined according to the NCEP ATP III criteria which were revised in 2005 (Grundy *et al.*, 2005) with ethnic specific cutoff values for waist circumference. The criteria are

Abdominal obesity (waist circumferences): men ≥ 90 cm; women ≥ 80 cm.

Triglycerides ≥ 150 mg/dl (≥ 1.7 mmol/L) or drug treatment for elevated triglycerides

HDL cholesterol: men <40 mg/dl (<1.0 mmol/L); women <50 mg/dl (<1.3 mmol/L) or drug treatment for low HDL cholesterol

Blood pressure $\geq 130/85$ mmHg or drug treatment for hypertension

Fasting glucose ≥ 100 mg/dl (5.6 mmol/L) or drug treatment for elevated blood glucose

For South Asia and Chinese patients waist circumference 90 cm or more for men and 80 cm or more for women. Diagnosis of metabolic syndrome is made when 3 or more of the risk factors present in an individual patient

Lab parameters: All parameters were measured on fresh serum sample drawn after at least 8 hours of fasting. Commercial enzymatic tests (Roche Diagnostics) were used for determining serum total cholesterol (TC), triglycerides (TG), and HDL-C concentrations. Fasting blood glucose was determined by an enzymatic colorimetric assay using a modified glucose oxidase-peroxidase method (Roche Diagnostics, Germany). Serum highly sensitive C-reactive

protein levels were estimated on random serum samples by Roche automated analyzers by Immuno Turbidometric assay for the invitro quantitative determination hs CRP in serum. Hs-CRP plasma levels were defined high when lab values were >3 mg/L.

Anthropometry: Height and weight were measured with standard instruments in light cloths with bare foot. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Waist circumference was measured to the nearest 0.5 cm by using a non-elastic plastic tape, just above the anterior superior iliac spine as defined according to the NIH protocol. Patients who were having acute illness, evidence of infection and others like Renal failure (acute or chronic), Connective tissue disorders (RA, SLE...etc), Systemic vasculitides, Gout, Trauma, Fever or evidence of any recent infections in the past 1 month, Malignancies, Congestive heart failure, Endocrine disorder (thyroid, crushing's syndrome etc) were excluded from the study.

Statistical analysis: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented on Mean \pm SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data. Significant figures + Suggestive significance (P value: $0.05 < P \leq 0.10$) *Moderately significant (P value: $0.01 < P \leq 0.05$) **Strongly significant (P value: $P \leq 0.01$).

RESULTS

Among 100 patients who were satisfying the modified ATP III criteria of metabolic syndrome for Asian Indians, 71% were men and 29% women with a mean age of 67.37 ± 6.32 years. The prevalence of Hypertension was 91%, elevated Waist circumference observed in 84%, Diabetes mellitus 81%, low HDL cholesterol 81% and elevated triglycerides 75% of the study population. All these risk factors were more prevalent in women than in men with no statistical significance ($p > 0.05$). Over all, the prevalence of high hs CRP was 60%. The value of hs CRP increased with 3, 4 and 5 of the risk factors in an individual patient ($p = 0.077$). In subjects with MS, the most frequent ATP-III MS component was hypertension, followed by increased waist circumference, hyperglycemia, low HDL-C levels and hypertriglyceridemia. (Table 1) To further investigate the interaction among MS components, the association between hs.CRP levels and all possible combinations of MS components was tested in regression analysis adjusted for age and gender. Only two combinations (namely: (1) hypertension + hyperglycemia + increased waist circumference ; (2) low-HDL + hypertension + increased waist circumference) were significantly associated with hs.CRP levels ($p < 0.037$ and 0.087 respectively). In the present study majority of elderly individuals with MS were affected by hypertension and elevated waist circumference and these two criteria were actually shared by these two MS phenotypes. The above results reflecting that Hypertension and Elevated Waist circumference leading to the variations in plasma highly sensitive C-reactive protein than other components of the ATPIII criteria of Metabolic syndrome in this elderly population.

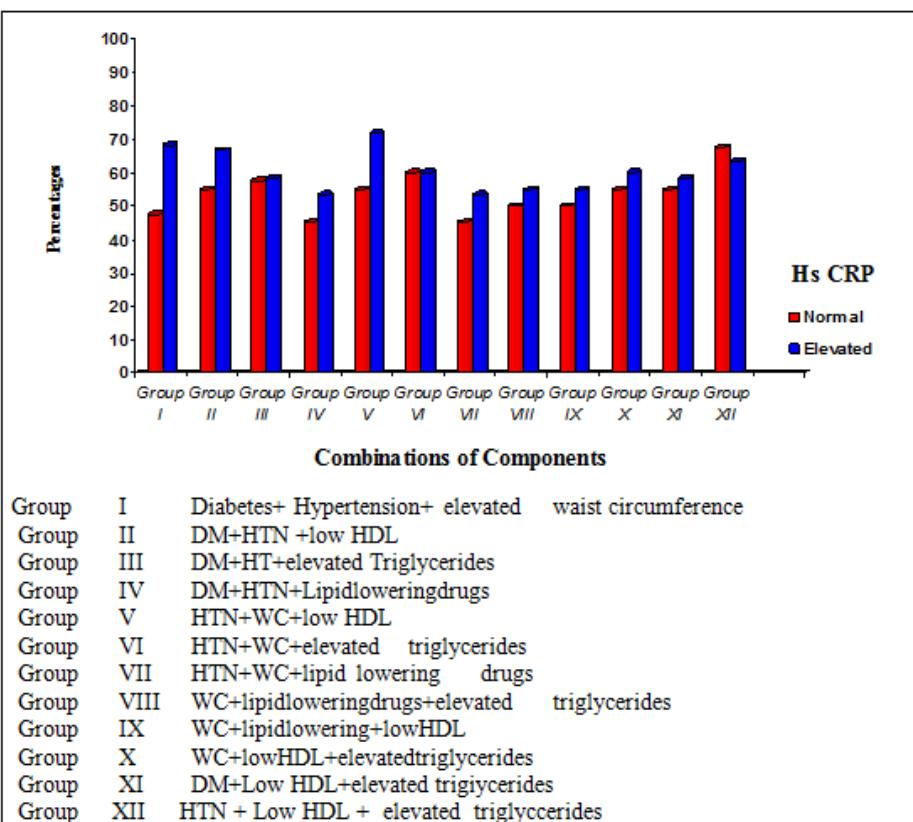
Table 1. Prevalence of various risk factors in the study group (ATP III revised criteria of MS)

ATP III	Total (n=100)		Male (n=71)		Female (n=29)	
	No	%	No	%	No	%
1.Abdominal obesity (WC \geq 90cm for men WC \geq 80 cm for women)	84	84.0	57	80.3	27	93.1
2.Triglycerides >150 mg/dl or using lipid lowering drugs	75	75.0	52	73.2	23	79.3
3.Low HDL-C or using lipid lowering drugs	81	81.0	55	77.5	26	89.6
4.BP \geq 130/85 or already on anti HTN drugs	93	93.0	65	91.5	28	96.6
5.Fasting glucose \geq 100 mg/dl or on diabetic drugs	81	81.0	58	78.8	23	79.3

P>0.05 (non of the component were significant between male and female)

Table 2. Association of risk factors with hs CRP

Variable	Total no. patients	CRP-(%)	CRP+ (%)	p value
Diabetes	Absent	19	17.5	0.755
	Present	81	82.5	
Hypertension	Absent	9	17.5	0.028
	Present	91	82.5	
Abdominal obesity	Normal	16	26.8	0.0138
	Elevated	84	73.2	
Triglycerides	Normal	72	70	0.716
	Elevated	28	30	
HDL Cholesterol	Normal	38	40	0.737
	Low	62	60	



DISCUSSION

We investigated the association of Metabolic syndrome and its components with presence of elevated hs. CRP levels (\geq 3 mg/L) by using data from a sample of one hundred elderly individuals attending a tertiary care hospital. Amongst the many definitions used to define the metabolic syndrome, the more frequently used was the National Cholesterol Education Program Adult treatment panel III (NCEP ATP-III) (Grundy *et al.*, 2005). In the absence of specific definition of MS in the elderly, we have chosen ATP III definition as a definition of MS as previously reported in the few studies in elderly subjects (Giovanni Zuliani *et al.*, 2009; Dupuy *et al.*, 2007). In our study, we evaluated the prevalence of various components of the metabolic syndrome with revised ATP III criteria for

Asian Indians (Grundy *et al.*, 2005) which included the modification of waist circumference with a lower cutoff. The components of the metabolic syndrome were correlated with a novel marker of systemic low grade inflammation which was "highly sensitive C-reactive protein (hs CRP)". Systemic inflammation had been closely associated with the pathogenesis of metabolic syndrome (Dupuy *et al.*, 2007). The mean age of our study population was 67.37 ± 6.32 years and it was lower compared to previous studies (69.3 years in the Dupuy *et al.* (2007) and 79.9 ± 8.6 years Giovanni Zuliani *et al.*, 2009). In our study 45% of the patients were satisfying all the 5 criteria of metabolic syndrome, 30% satisfied 4 criteria. Among the MS criteria, the prevalence of hypertension and increased waist circumference was significantly higher, while the

prevalence of hyper triglyceridemia was lower in individuals with high hs. CRP. Hs CRP was considered to be elevated if it was 3 mg/dl or more according the various previous studies conducted in elderly (Giovanni Zuliani et al., 2009; Dupuy et al., 2007; Cankurtaran et al., 2006). Hs CRP was elevated in 60% of our patients and such elevation was more common in females (75.9%) than the males (53.5%). This was similar to a study conducted by Ming-May Lai et al. (2010) in Taiwan. This finding suggested that systemic inflammation may be more common in females than males.

In our study population various components of the MS, were associated with varying elevation of hs CRP. It was also observed that 40% of MS subjects in contrast had low hs CRP. It could be suggesting the possibility that not only the individual components of MS but also other unmeasured markers may be associated more strongly with elevated hs CRP independently. Amongst the components of MS, waist circumference (Giovanni Zuliani et al., 2009; Dupuy et al., 2007) and Hypertension were significantly associated with elevated hs CRP levels irrespective of gender. This suggests that visceral obesity and Hypertension were the major determinants of elevated hs CRP levels in elderly subjects with MS, which was similar to a study conducted by Giovanni et al. (2009) and another Indian study conducted by Panniyammakal et al. (2011) in a middle aged subjects. In contrast the other components of MS such as high Triglycerides, low HDL cholesterol and Diabetes mellitus or fasting hyper glycemia did not show any statistically significant association with hs CRP levels in elderly with MS. In an Italian study by Giovanni et al (Giovanni Zuliani et al., 2009) reported that waist circumference was closely correlated with the level of abdominal visceral adipose tissue and related metabolic variables, in both sexes. Waist circumference was a simple measurement that estimates the extent of abdominal obesity, which was closely linked to the deposition of visceral fat (Giovanni Zuliani et al., 2009). Sub cutaneous fat had no significant association with hs CRP as reported by Giovanni et al. (2009). Hypertension and duration of the Hypertension were showing statistically significant association with elevated hs CRP in our study population in univariate analysis. Longer the duration of Hypertension higher the elevation of hs CRP. Elevated Systolic blood pressure or Diastolic blood pressure was not showing any statistical significance individually, which was in contrast to that in previously reported studies by Tamakoshi et al. (2003), where they have shown a significant association with SBP & DBP and an Indian study by Panniyammakal Jeemon et al. (2005).

Festa et al. (2000) in the Insulin Resistance and Atherosclerosis Study (IRAS), showed that hs CRP was positively correlated with BMI, waist circumference, blood pressure, triglycerides, total cholesterol, LDL cholesterol, plasma glucose, and fasting insulin, but it was inversely correlated with HDL cholesterol and the insulin sensitivity index. The strongest associations were observed between CRP levels, central adiposity, and insulin resistance. Higher the number of risk factors in an individual patient higher the elevated hs CRP which was similar to a study done by Tamakoshi et al. (2003) In our study we observed similar findings i.e elevated plasma hs CRP levels were positively correlated to waist circumference, hypertension, BMI, elevated total cholesterol, elevated LDL cholesterol. In our study strongest correlation with elevated hs CRP was found with Hypertension and its duration, waist circumference, BMI.

Conclusion: The results of our study concluded that of all the components of Metabolic syndrome, Hypertension and visceral adiposity were observed more frequently than the occurrence of other components in this elderly cohort of South India. Among five components of metabolic syndrome elevated waist circumference and hypertension were most commonly associated with systemic inflammation as measured by elevated hs CRP. Higher the number of risk factors in a individual patient higher the elevated hs CRP.

Limitations: Due to the study's cross-sectional nature, our results do not establish causality. Subjects taking anti diabetic and lipid lowering agents were not excluded from our study, which might have influenced the CRP levels. As it was a hospital population based study there may be referral bias.

Financial disclosure: Nothing to disclose

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