

Association of High Levels of High-Sensitive C-Reactive Protein with Metabolic Syndrome- A Cross-Sectional Study

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ABSTRACT

Introduction: Elevated high-sensitivity C-Reactive Protein (hsCRP) might be associated with prolonged low inflammation stage like Metabolic Syndrome (MetS) and also predicts onset of Cardiovascular Disease (CVD) and diabetes mellitus. Precise association of hsCRP with occurrence of MetS among Western part of India is less clear.

Aim: To evaluate serum hsCRP level in MetS patients and its association with occurrence of MetS, components of MetS and demographic variables.

Materials and Methods: This was a hospital based cross-sectional study, carried out on 86 cases of MetS and 86 age and sex matched apparently healthy controls for a duration of 20 months in Grant Government Medical College and Associated Hospital, Mumbai. The detailed history including alcohol consumption and smoking, Waist Circumference (WC), Systolic and Diastolic Blood Pressures (SBP, DBP) were taken from all the study participants. Diagnosis of MetS was done according to revised National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. About 5 ml

venous blood was collected by venepuncture for measurement of hsCRP, Fasting Blood Glucose (FBG), Triglyceride (TAG) and HDL-C. Chi-square test, unpaired t-test, one-way ANOVA and multivariate linear regression model were used for statistical analysis by using SPSS 16.0 software. The p-value of <0.05 was taken as statistically significant.

Results: Mean value of hsCRP was 4.97 ± 1.48 mg/L and 2.99 ± 1.20 mg/L in MetS cases and controls, respectively. The mean difference of hsCRP was statistically highly significant ($p < 0.001$). The hsCRP level of >3.0 mg/L (OR= 5.8, CI=2.68-13.5, $p < 0.001$) and 1-3 mg/L (OR= 2.6, CI=1.24-6.19, $p < 0.01$) were significantly associated with MetS. The hsCRP was significantly higher in older age groups ($p < 0.001$), heavy alcohol use ($p < 0.01$), WC ($p < 0.003$) and FBG ($p < 0.03$) in MetS cases. Serum hsCRP level was independently positively associated with age ($\beta = 0.26$, $p = 0.01$), WC ($\beta = 0.33$, $p = 0.001$) and FBG ($\beta = 0.25$, $p = 0.02$) in MetS cases.

Conclusion: The hsCRP was significantly associated with MetS syndrome particularly in cases with high WC and fasting blood sugar.

Keywords: Alcohol use, Cardiovascular disease, Fasting blood glucose, Waist circumference

INTRODUCTION

Metabolic Syndrome is a rising health concern in a developing country like India [1]. According to various epidemiological studies, prevalence of MetS is around 30-40% in India [2,3]. Urbanisation, sedentary life, stress, obesity, changes in dietary habits and genetic phenotypes are key important factors for increasing prevalence [4]. MetS is constellation of various anthropometric, biochemical and metabolic abnormalities. MetS is characterised by presence of central obesity, abnormal glucose levels, elevated blood pressure and dyslipidemia [5]. MetS has been strongly associated with increased risk for development of diabetes mellitus and CVD in future [6]. Presence of chronic inflammation and insulin resistance are thought to be important factors for development of MetS [7]. Increased circulating blood level of TNF- α by adipocytes are considered for development of chronic inflammation and insulin resistance in MetS [8].

Assessment of blood pressure and lipid profile are simple tools to predict CVD [9]. Currently, hsCRP has emerged as a novel marker to identify and predict vascular inflammation and cardiovascular events in high risk patients like MetS [10]. CRP is an acute phase reactant synthesised mainly in liver in response to inflammatory processes. It has a long plasma half-life of around 18-20 hours and its circulating level is not influenced by intake of food and diurnal variation [11]. Currently, available highly sensitive methods measure CRP at a very narrow range of concentration from 0.01 to 10 mg/L [12]. The hsCRP identifies inflammation competently and also helps to deal with the risk related to inflammation [13]. According to new research data, it has been suggested that low level of hsCRP is

associated with less cardiovascular events rather than low level of LDL-C [14]. High hsCRP level (>2 mg/L) has been associated with occurrence of recurrent myocardial infarction [15]. High hsCRP is strongly associated with prolonged low inflammation stage like MetS and also predicts commencement of cardiovascular events and diabetes mellitus [16].

Precise association of hsCRP with occurrence of MetS among Western part of India is less clear [17,18]. There is a necessity of a biomarker that predicts MetS and cardiovascular events among high risk populations. High level of hsCRP might be an individual component of MetS and associated with MetS. Thus, the aim of this study was to evaluate serum hsCRP level in MetS patients and its association with occurrence of MetS, components of MetS and demographic variables.

MATERIALS AND METHODS

This hospital based cross-sectional study was carried out on 86 cases of MetS and 86 age and sex matched apparently healthy controls in Biochemistry and Medicine Departments of Grant Government Medical College, Mumbai. Patients attending Medicine OPD for health checkup from March 2014 to October 2016 were selected by convenient sampling who met the inclusion criteria of the study. Based on the pilot study, the hsCRP levels of 20 MetS cases were first checked. Out of 20 cases, it was found that 5 cases had increased hsCRP level (6.4 mg/L, 10.4 mg/L, 3.24 mg/L, 3.1 mg/L and 6.9 mg/L). So, prevalence of elevated hsCRP among MetS cases was found to be 25.0%. Based on 25.0% prevalence, sample size of this study was calculated by the formula: Sample size (N) =

(Z₂) (pq)/L₂ (Z=Confidence interval, p=prevalence, q=1-prevalence and L=absolute error of 10%). Based on this formula, sample size of 82 was taken. The study was approved by the Institutional Human Ethics Committee (NO.IEC/Pharm/88/2014). The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all study participants. The detailed history, clinical findings and laboratory findings of each study participant like age, sex, alcohol use, smoking habits, height, weight, WC, FBG, TAG, SBP, DBP, and hsCRP were recorded in a prepared proforma of the study. Participants presenting with history of no alcohol use during their lifetime and lifetime abstainers (fewer than 12 drinks in lifetime) were considered in category of no drinking [19]. Participants presenting with history of casual or social drinking or alcohol drinking up to three times a week were considered in category of occasionally drinking [20]. Upto two drinks per day for men and upto one drink for women was considered as moderate drinking [21]. Five or more days of binge drinking in one month was considered as heavy drinking. Consumption of four drinks for women and five drinks for men in duration of two hours was called binge drinking [21]. A participant who had smoked 100 cigarettes during lifetime and who currently smoked cigarettes was considered as a current smoker. A participant who had never smoked or had smoked <100 cigarettes during lifetime was considered as a non smoker [22].

Diagnosis of Metabolic Syndrome (MetS): Diagnosis of MetS was done according to revised NCEP ATP III criteria (National Cholesterol Education Program, Adult Treatment Panel III) [23]. Patients presenting with any of the following three factors out of five factors were considered as cases: abdominal obesity (increased WC in men >40 inches and in women >35 inches), high FBG (>100 mg/dl or on regular drug treatment for high FBG), high TAG (>150 mg/dL or on regular drug treatment for high TAG), low HDL-C (≤40 mg/dL for men, ≤50 mg/dL for women), high blood pressure (>135/85 mmHg or on regular drug treatment for high blood pressure) [23].

Inclusion Criteria

MetS patients of any gender and age between 30-60 years were included in the study.

Exclusion Criteria

Patients presenting with history of coronary artery disease, type 1 diabetes mellitus, peripheral vascular diseases, hypothyroidism, rheumatoid arthritis, any chronic infectious and inflammatory diseases, any type of malignancy, stroke, pregnancy and women on oral contraceptive pills were excluded from the study.

Measurement of parameters and collection of blood: WC was measured using a non stretchable measuring tape at the point of widest circumference area between superior border of iliac crest and lower rib during expiration and inspiration in standing position and an average of two measurements was considered as final WC [24]. Blood pressure was measured by using a mercury sphygmomanometer on left arm in sitting position after 10 minutes of rest and average of three readings taken at 5 minutes interval was considered as final SBP and DBP recordings. Explanation of the procedure and minor discomfort of cuff inflation were explained to all participants to reduce fear and anxiety. Following conditions were fulfilled before blood pressure measurements: no smoking, alcohol, heavy meal in last 30 minutes, back supported and arm supported on table, void bladder before measurement, legs uncrossed and both feet touching the ground.

About 5 mL of venous blood was collected from peripheral vein by venepuncture under aseptic condition after 12 hours overnight fasting from all cases and controls. About 3 mL blood was transferred to a plain vacutainer for estimation of TAG, HDL-C and hsCRP. About 2 mL was transferred to sodium fluoride vacutainer for FBG estimation. Serum was separated by centrifuge plain vacutainer at 3000 rpm for 10 minutes.

Analysis of serum hsCRP was done on immulite-1000 chemiluminescent auto analyser by using kits of Siemens Health Care Diagnostics, LA, California, USA. To find association of hsCRP with MetS, participants were divided into the following groups according to hsCRP levels, <1 mg/L, 1-3 mg/L and >3 mg/L and considered as low, intermediate and high risk groups, respectively [25]. Analysis of FBG, TAG and HDL were done on ADVIA 1800 chemistry auto analyser from Siemens Health Care Diagnostics, LA, California, USA.

STATISTICAL ANALYSIS

Statistical analysis was done with the help of SPSS version 16. Numerical variables were reported as frequency, percentage, mean and standard deviation. Chi-square test was used to compare qualitative variables and unpaired-t-test was used to compare quantitative variables. One-way ANOVA was used to compare means in different groups. Odds ratio and 95% CI was calculated by conditional logistic regression. Association of hsCRP with demographic variables and components of MetS was calculated by multivariate logistic regression analysis. All the study participants were adjusted for gender, age, alcohol use, smoking and components of MetS. The p-value of <0.05 was taken as statistically significant.

RESULTS

Male participants (n=45, 52.3%) were more as compared to females (n=41, 47.7%) in MetS cases. Similarly, male participants (n=44, 55.1%) were more as compared to females (n=42, 48.8%) in control group. MetS was found more in the age group of 40-50 years (n=31, 36.1%) compared to age group of 30-40 years (n=26, 30.2%) and 50-60 years (n=29, 33.7%). There was no statistically significant difference in distribution of cases and controls according to gender (p=0.87), age (p=0.98), alcohol use (p=0.55) and smoking (p=0.73) [Table/Fig-1].

Parameters	MetS cases Frequency n (%)	Controls Frequency n (%)	Chi-square statistic	p-value
Gender				
Men	45 (52.3%)	44 (51.1%)	0.02	0.87 NS
Women	41 (47.7%)	42 (48.8%)		
Age				
30-40 years	26 (30.2%)	27 (31.4%)	0.03	0.98 NS
40-50 years	31 (36.1%)	31 (36.1%)		
50-60 years	29 (33.7%)	28 (32.5%)		
Alcohol use				
No drinking or occasionally	40 (46.5%)	42 (48.8%)	1.18	0.55 NS
Moderate drinking	31 (36.0%)	34 (39.5%)		
Heavy drinking	15 (17.5%)	10 (11.7%)		
Smoking				
Non smoker	62 (72.1%)	64 (74.4%)	0.11	0.73 NS
Current smoker	24 (27.9%)	22 (25.6%)		

[Table/Fig-1]: Baseline characteristics of the study participants.

Chi-square test was used to calculate p-value; *p-value <0.05 significant; **p-value <0.001 HS (highly significant); NS: Not significant

Mean values of WC, FBG, TAG, HDL-C, SBP and DBP were significantly high in MetS cases compared to controls (p<0.001**). Mean value of hsCRP was 4.97±1.48 mg/L and 2.99±1.20 mg/L in MetS cases and controls, respectively. The hsCRP level was significantly high in MetS patients compared to controls. (p<0.001**) [Table/Fig-2].

Cases with high hsCRP level (>3.0 mg/L) had significant difference with respect to numbers of MetS cases (p<0.001**), mean age (p<0.001**), heavy drinking habit (p<0.01*), high WC (p<0.003*) and high FBG (p<0.03*) compared to group with hsCRP ≥1.0-≥3.0 mg/L and <1.0 mg/L [Table/Fig-3]. Any significant association of

hsCRP with demographic variables and components of MetS in control was not found [Table/Fig-4].

Variables	MetS cases Mean±SD	Controls Mean±SD	p-value
Age (years)	48.47±6.72	50.12±7.29	0.12 NS
Waist circumference (Inches)	41.19±3.16	35.15±4.18	<0.001** HS
Fasting blood glucose (mg/dL)	135.62±39.01	93.58±14.16	<0.001** HS
Triglycerides (mg/dL)	199.08±53.80	118.89±33.68	<0.001** HS
HDL-Cholesterol (mg/dL)	35.49±10.23	47.25±7.29	<0.001** HS
Systolic blood pressure (SBP) (mm of Hg)	141.29±21.92	117.29±11.25	<0.001** HS
Diastolic Blood pressure (DBP) (mm of Hg)	91.62±13.45	79.58±8.25	<0.001** HS
hsCRP (mg/L)	4.97±1.48	2.99±1.20	<0.001** HS

[Table/Fig-2]: Comparison of demographic variables, MetS components and hsCRP among cases and controls. Unpaired t-test was used to calculate p-value; *p-value <0.05 significant; **p-value <0.001 HS (highly significant); NS: Not significant

Variables	hsCRP (mg/L)			p-value
	<1.0 mg/L (n=15)	1.0-3.0 mg/L (n=28)	>3.0 mg/L (n=43)	
MetS, n (%)	15 (17.4%)	28 (32.6%)	43 (50.0%)	†0.001**
Controls, n (%)	40 (46.5%)	27 (31.4%)	19 (22.1%)	
Age (years, mean±SD)	44.52±4.00	47.8±5.10	50.92±6.89	‡0.001**
Alcohol (n) (%)				
No drinking	10 (11.6)	11 (12.8)	11 (12.8)	†0.01*
Moderate drinking	3 (3.4)	15 (17.5)	20 (23.2)	
Heavy drinking	2 (2.4)	2 (2.4)	12 (13.9)	
Smoking (n) (%)				
No smoking	10 (11.6)	16 (18.7)	25 (29.1)	†0.82 NS
Current smoking	5 (5.8)	12 (13.9)	18 (20.9)	
WC (Inches, mean±SD)	36.25±3.99	38.96±4.89	42.01±6.92	†0.003*
FBG (mg/dL, mean±SD)	110.93±16.51	121.56±20.57	129.81±26.73	†0.03*
TAG (mg/dL, mean±SD)	193.03±45.2	197.9±48.9	194.4±50.23	†0.93 NS
HDL-C (mg/dL, mean±SD)	36.91±8.23	36.25±7.01	34.92±9.77	†0.68 NS
SBP (mmHg, mean±SD)	136.25±11.2	140.01±19.4	141.2±15.57	†0.60 NS
DBP (mmHg, mean±SD)	88.24±12.21	89.71±10.3	92.23±11.2	†0.41 NS

[Table/Fig-3]: Distribution of demographic variables, MetS components according to different hsCRP group in MetS cases.

†Chi square test and ‡one-way ANOVA were used to calculate p-value; *p-value <0.05 significant, **p-value <0.001 HS (highly significant); NS: Not significant

The association between hsCRP levels in all individuals and occurrence of MetS are described in the [Table/Fig-5]. Compared to individual with hsCRP level of <1.0 mg/L, the odds ratio increased from 2.6 (CI=1.24-16.19, p<0.01*) to 5.8 (CI=2.68-13.5, p<0.001**) in the groups with hsCRP levels of ≥1.0-≥3.0 mg/L and >3.0 mg/L, respectively. Thus, association of MetS increased with high levels of serum hsCRP [Table/Fig-5]

In multivariate linear regression model [Table/Fig-6], serum hsCRP level was independently positively associated with age ($\beta=0.26$, $p=0.01^*$), WC ($\beta=0.33$, $p=0.001^{**}$) [Table/Fig-7] and FBG ($\beta=0.25$, $p=0.02^*$) [Table/Fig-8] in MetS cases. All the cases were adjusted for gender, age, alcohol use, smoking and components of MetS.

Variables	hsCRP (mg/L)			p-value
	<1.0 mg/L (n=40)	1.0-3.0 mg/L (n=27)	>3.0 mg/L (n=19)	
Age (years, mean±SD)	46.93±6.83	48.2±5.21	50.1±8.91	†0.25 NS
Alcohol n (%)				
No drinking	21 (24.4)	21 (24.4)	8 (9.3)	†0.12 NS
Moderate drinking	15 (17.6)	4 (4.6)	8 (9.3)	
Heavy drinking	4 (4.6)	2 (2.3)	3 (3.5)	
Smoking n (%)				
No smoking	35 (40.7)	24 (27.9)	16 (18.6)	†0.89 NS
Current smoking	5 (5.82)	3 (3.4)	3 (3.4)	
WC (Inches, mean±SD)	34.27±4.23	33.91±5.78	35.12±6.85	†0.71 NS
FBG (mg/dL, mean±SD)	92.58±14.16	95.72±17.27	94.9±14.31	†0.63 NS
TAG (mg/dL, mean±SD)	117.26±23.67	118.61±30.12	116.5±17.9	†0.95 NS
HDL-C (mg/dL, mean±SD)	46.29±5.21	44.25±8.53	43.85±7.92	†0.34 NS
SBP (mmHg, mean±SD)	115.3±10.2	118.72±9.39	120.32±8.55	†0.13 NS
DBP (mmHg, mean±SD)	78.57±8.12	81.83±9.86	80.92±13.35	†0.40 NS

[Table/Fig-4]: Distribution of demographic variables, MetS components according to different hsCRP group in controls groups.

†Chi-square test and ‡one-way ANOVA were used to calculate p-value; *p-value <0.05 significant; **p-value <0.001 HS (highly significant); NS: Not significant

hsCRP level	MetS cases n (%)	Controls n (%)	Adjusted OR ^a	CI ^b	p-value
<1.0 mg/L	15 (17.4%)	40 (46.5%)	1.0 (ref.)	-	-
≥1.0-≥3.0 mg/L	28 (32.6%)	27 (31.4%)	2.6	1.24-6.19	0.01*
>3.0 mg/L	43 (50.0%)	19 (22.1%)	5.8	2.68-13.5	0.001** HS

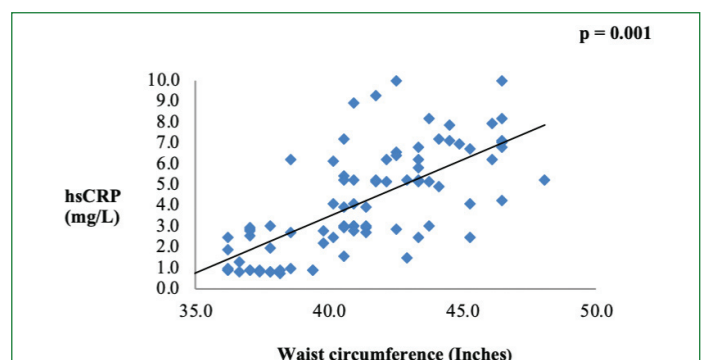
[Table/Fig-5]: Odds ratio and 95% CI of hsCRP in cases and controls.

^aConditional logistic regression was used to calculate OR and 95% CI; *p-value <0.05 significant; **p-value <0.001 HS (highly significant); NS: Not significant

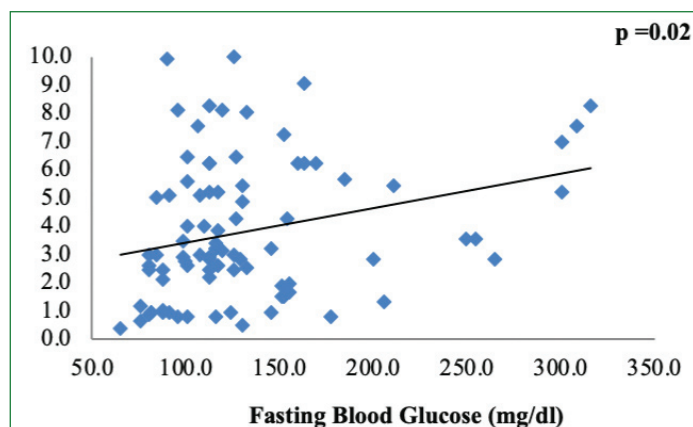
Variables	HsCRP	
	Regression coefficient (β)	p-value
Age	0.26	0.01*
Waist circumference	0.33	0.001** HS
Fasting blood glucose	0.25	0.02*
Triglycerides	0.076	0.35 NS
HDL-Cholesterol	0.10	0.34 NS
Systolic blood pressure	0.003	0.79 NS
Diastolic Blood pressure	0.002	0.98 NS

[Table/Fig-6]: Association of hsCRP with demographic variables and components of MetS in MetS cases.

Multivariate linear regression was used to calculate p-value; *p-value <0.05 statistically significant; **p-value <0.001 HS (highly significant); NS: Not significant



[Table/Fig-7]: Scatter plot with linear regression of hsCRP with Waist Circumference (WC).



[Table/Fig-8]: Scatter plot with linear regression of hsCRP with Fasting Blood Glucose (FBG) level.

DISCUSSION

Assessment of cardiovascular risk factor is important in MetS to reduce future mortality and morbidity in these patients. hsCRP has a high specificity and a potential role to predict CVD [26]. Strong linkage has been observed between inflammation and increased hsCRP level [27]. Various studies have been carried out to find the association between hsCRP and MetS. But results have been conflicting. Sah SK et al., observed the association of hsCRP with MetS components and found hsCRP was positively correlated with blood glucose ($r=0.2$, $p=0.026^*$) and negatively correlated with HDL cholesterol ($r=-0.361$, $p<0.001^{**}$) [28]. However, Chowta MN et al., reported no significant correlation of hsCRP with blood glucose, TAGs, LDL and HDL cholesterol [29].

In the present study, mean value of hsCRP was significantly higher (p -value $<0.001^{**}$ HS) in MetS cases (4.97 ± 1.48 mg/L) compared to controls (2.99 ± 1.20 mg/L). It was observed that 50.0% cases had significantly high hsCRP (>3 mg/L). Chronic low-grade inflammation in MetS produce more cytokines like IL-1, IL-6, TNF- α that cause an increase in the synthesis of CRP in liver [30]. Gowdaiah PK et al., reported similarly high mean values of hs-CRP (8.3 ± 1.04 Vs 1.6 ± 0.79 mg/L, p -value $<0.001^{**}$) in MetS cases and controls, respectively [31] and Florez H et al., also observed increased CRP values among MetS cases (4.85 ± 0.47 mg/L Vs. 3.34 ± 0.36 mg/L, $p<0.05^*$) [32]. High hsCRP was significantly associated with increase in WC and FBG. Silvia F et al., demonstrated an independent association of WC with high CRP of >3.0 mg/dL (OR 3.0, $p=0.01^*$) [33].

Significant independent positive association of hsCRP with age was observed ($\beta=0.26$, $p=0.01^*$). Positive correlation of hsCRP with age is acceptable as there is age related increase in chronic sub inflammation due to immunosenescence [34]. Wang Z, et al., also observed an independent positive association of the high hsCRP (>1.80 mg/L) with age ($p<0.05^*$) [35]. An independent positive association of hsCRP with WC was found ($\beta=0.33$, $p=0.001^{**}$). Adipose tissues highly express inflammatory cytokines like IL-6. More deposition of adipose tissue (increase WC) cause more production of IL-6 and result in increase synthesis of CRP in liver [36]. We have also observed significant positive association between hsCRP and FBG level ($\beta=0.25$, $p=0.02^*$). Normally, insulin inhibits production of inflammatory cytokine and CRP production. This inhibition process does not occur in insulin resistance (indirectly high blood sugar) and may be responsible for high CRP production [37]. Niehoff AG et al., reported independent positive association of hsCRP with FBG level ($\beta=0.57$, $p\leq 0.001^{**}$) [38]. Thus, hsCRP has been independently associated with age, WC and FBS in multivariate analysis model. A significant difference was found between various hsCRP groups with increasing alcohol consumption. Excessive alcohol use cause increase in inflammation at tissue level and lipid peroxidation by free radical generation, because of direct inflammatory effect of excess ethanol on hepatocytes [39]. Increase LDL oxidation, decrease

nitric oxide expression and decrease fibrinolysis by CRP are mainly responsible for development of CVD [40]. Hence, high serum level of hsCRP may be associated with MetS and it can be used as simple and cost-effective screening tool to evaluate MetS.

Limitation(s)

Although the inclusion and exclusion criteria was strictly followed for enrollment of study participants and all study participants were standardised for demographic characteristics and components of MetS, small sample size and a hospital-based study were the limitations of the study. Population based multicentric follow-up study along with measurement of insulin and pro inflammatory cytokines should be done to further validate the study findings.

CONCLUSION(S)

Serum hsCRP was significantly high in patients with MetS compared to healthy controls and high hsCRP level was significantly associated with MetS. Serum hsCRP was independently associated with age, WC and FBG level. hsCRP can be used as a screening marker for MetS particularly with high WC and FBG.

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