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The prevalence of metabolic syndrome increases with serum hs-CRP concentration in individuals without a history of cardiovascular disease: A report from a large Persian cohort

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Abstract

Background

Metabolic syndrome (MetS) is defined by a clustering of cardiovascular (CV) risk factors, and associates with a heightened inflammatory state. A raised serum high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, is also known to associate with CV risk. We have investigated the relationship between the presence of MetS and serum hs-CRP in a large representative Persian population cohort without a history of cardiovascular disease (CVD).

Methods

The MASHAD study population cohort consisted of 9,778 subjects, who were recruited from the city of Mashhad, Iran, between 2007 and 2008. Several CV risk factors were measured in this population without CVD. Individuals were categorized into quartiles for serum hs-CRP: the quartiles had median and IQR for serum hs-CRP of 0.72 (0.59-0.85) mg/L, 1.30 (1.14-1.4) mg/L, 2.29 (1.92-2.81) mg/L and 6.63 (4.61-11.95) mg/L respectively. The prevalence of MetS in each quartile was determined using either **International Diabetes Federation** (IDF) or **Adult Treatment Panel III** (ATPIII) criteria.

Results:

The prevalence of MetS was highest in the 4^{th} quartile for serum hs-CRP [1220 (50.0%)], and significantly higher than for the 1^{st} quartile (reference group) [634 (25.9%)] ($p<0.001$). A positive smoking habit [OR, 1.47 (1.26-1.70), $p<0.001$] and the presence of either MetS-IDF [OR, 1.35 (1.18-1.55), $p<0.001$] or Mets-ATPIII [OR, 1.40 (1.18-1.50), $p<0.001$] were strong predictors for being in the 4^{th} quartile for serum hs-CRP.

Conclusions:

There was a significant association between high levels of serum hs-CRP and the presence of MetS among individuals without a history of CVD in our Persian cohort.

Introduction:

Metabolic syndrome (MetS) is defined by a clustering of several known cardiovascular (CV) risk factors. [1] These include obesity, dyslipidemia and impaired glucose tolerance, and the presence of MetS is therefore associated with a high risk of subsequent CV disease (CVD). [2] MetS has a high prevalence [3-5] and is a serious public health concern in Iran.

High sensitivity C-reactive protein (hs-CRP), is an indicator of a heightened inflammatory state, and also appears to be a useful biomarker of CVD risk in both Western [6,7] and Iranian societies. [8,9] There have been strong recommendations to use serum hs-CRP in CVD risk assessments. [10,11]

The inflammatory state associated with MetS may contribute to the atherosclerotic process and use of serum hs-CRP in individuals with MetS has been discussed previously. [12] We wished to determine whether, in individuals without a history of CVD, serum hs-CRP was a discriminant for the presence of MetS.

Material and Methods:

Subjects

The study population was recruited between 2007-2008 using a stratified-cluster method and derived from an ongoing cohort named 'Mashhad stroke and heart atherosclerosis disorder' (MASHAD) study, Mashhad, Iran. The minimum and maximum age of the subjects was 35 and 64 years respectively. The main inclusion criterion for this study was the absence of a past history of a CV event (unstable angina, myocardial infarction and stroke), heart failure, peripheral vascular disease including transient ischaemic attack or amaurosis fugax, or a history of any previous cardiovascular interventions or surgery; however, the presence of traditional

cardiovascular risk factors including dyslipidaemia, diabetes mellitus and hypertension were not used as exclusion criteria for the study. Individuals with any major co-morbidities such as cancer, autoimmune diseases (eg, systemic lupus erythematous, rheumatoid arthritis, multiple sclerosis), overt acute or chronic infectious disease, and inflammatory diseases at the time of recruitment were excluded. Each subject gave informed written consent to participate in the study, which was approved by the Mashhad University of Medical Science Ethics Committee.

For all subjects, clinical data were collected from their available records, questionnaires and face-to-face interview. Anthropometric measurements and standard blood pressure assessment were performed as previously described. [4]

Biochemical analysis

Plasma and serum were collected following a 12 h fast and stored at -80^{o}C. A fasting blood glucose (FBG) and full lipid profile were measured using enzymatic methods (Pars Azmun, Karaj, Iran). Serum hs-CRP concentration was measured by immunoturbidity (Pars Azmun, Karaj, Iran).

Metabolic syndrome

Both the International Diabetes Federation (IDF) and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) definitions of r MetS were used in our data analysis as previously described. [4] IDF-MetS was defined by the presence of three or more of the following components: fasting plasma glucose ≥6.1 mmol/L; systolic or diastolic blood pressure ≥130 or ≥85 mmHg; High-density lipoprotein cholesterol (HDL-C) 1.29 mmol/L for women or 1.03 mmol/L for men; triglyceride ≥1.70 mmol/L; and waist circumference ≥80 cm for women

or ≥94 cm for men. ATPIII-Mets was defined as being present when three of the following criteria were met:

Increased waist circumference: >102 cm for men and >90 cm for women; plasma concentration of HDL-C< 1.03mmol/L for men and 1.29 mmol/L for women; raised values for plasma triglycerides: 1.70 mmol/L ; systolic or diastolic blood pressure ≥130 or ≥85 mmHg; FBG ≥110 mg/dL(6.1 mmol/L)

Statistical analysis

Statistical analysis was performed using SPSS version 23(SPSS Inc., Chicago, IL, USA), Data were evaluated for normality using the Kolomogorov-Smirnov test. Student-t tests and Mann-Whitney tests were used to compare means or medians of variables with or without normal distribution respectively. Chi-square tests were used to compare the qualitative variables. Serum hs-CRP concentration distribution was divided into quartiles and patients in the 1st quartile (lowest level of hs-CRP) were considered as a reference group. Nominal regression analysis was used to predict whether serum hs-CRP was related to metabolic and traditional CV risk factors. Odds ratios (ORs) with 95% confidence intervals were obtained using regression analysis.

Results:

All data were available for the 9778 (of which 3611 [36.9%] were male) participants in this study,(Table 1). The median and interquartile ranges of hs-CRP in different quartiles were 0.72 (0.59-0.85) mg/L 1st quartile, 1.30 (1.14-1.4) mg/L 2nd quartile, 2.29 (1.92-2.81) mg/L 3rd quartile and 6.63 (4.61-11.95) mg/L 4th quartile (Table 1).

In all our univariate and multivariate analyses, the first quartile served as a reference group. Subjects in the 4th quartile were significantly older than those in the 1st quartile (49.0±8.3 y versus 46.9±8.2 y; p<0.0.001, Table 1). Several risk factors, including: blood pressure, lipid profile, body mass index and waist circumference, history of diabetes mellitus, hypertension, and current smoking status, showed increased with quartile (Table 1). The percentage of male participants was significantly lower in the 4th quartile (33.3%) compared to other quartiles, with the 1st quartile (47.0%) containing the highest % of male subjects (p<0.001).

The percentage of patients with IDF- MetS in the 1st , 2nd, 3rd and 4th quartiles were 25.9%, 35.0%, 44.7% and 50.0% respectively (p<0.001). Moreover, based on ATP-III criteria, the percentage of MetsS in each quartile were found to be 21.0%, 29.5%, 40.5% and 45.9% respectively (p<0.001).

Multivariate analysis showed that in all 2nd, 3rd, and 4th quartile groups compared to the reference group a positive current smoking habit and the MetS were the strongest determinants for quartile of hs-CRP. In the 4th quartile a positive current smoking habit gave an OR of 1.47 (1.26-1.70) compared to reference group, and for IDF-MetS and ATPIII-Mets the OR were 1.35(1.18-1.55)] and 1.40 (1.18-1.50) respectively (Table 2).

Discussion:

This was a cross-sectional study with a large sample size of subjects without a history of CVD. We found a significant worsening of several conventional CV risk factors in the individuals within the 4th quartile for serum hs-CRP compared to the subjects within the 1st quartile. The percentage of subjects with MetS within the 4th quartile was approximately two-fold higher than the reference group. This value was slightly greater using the ATPIII definition

of MetS versus the IDF definition. A high serum hs-CRP in the early phases of atherosclerosis is considered to reflect vascular inflammation, and its measurement has been advocated as an adjunct to the assessment of conventional risk factors. [13] The serum hs-CRP concentrations in asymptomatic individuals, was particularly high in a proportion of individuals; around 25% of subjects who were in the 4th quartile for serum hs-CRP had serum levels that were greater than 11.95 mg/L. Several studies with large sample sizes from both the United States and Europe have demonstrated that serum hs-CRP is useful for the prediction of future CV events among apparently healthy men and women [10].

The association between MetS and elevated levels of serum hs-CRP (>3 mg/L) has been shown in non-diabetic Cuban Americans (55 men and 106 women) aged ≥ 30 years. [14] Serum hs-CRP was also found to be significantly higher in the patients with MetS than in those without among the diabetic patients. [15] A study of 5,728 subjects with a similar mean age as our study showed that subjects with three, four, or five features of the MetS, had 5.1, 10.7 and 11.1 times greater odds of elevated hs-CRP (>3 mg/L) compared to subjects without any features of the MetS. [16] . Our results indicate that elevated levels of serum hs-CRP are associated with an increased prevalence of MetS, which is a cluster of known predisposing risk factors to CV events. Our results cannot show whether an increased serum hs-CRP is a cause or consequence of MetS, but highlights the high probability of a concurrent increase in inflammatory status and MetS. According to in-vitro studies as well as large sample evidence the association between hyper-inflammation (i.e., defined by increased CRP) and insulin resistance, adiposity and other features of MetS is known to be linked to further elevated risk of cardiovascular events. [17]

The cut off values of serum hs-CRP for Mets in our population differed with definition of the MetS and was 1.60 mg/L (IDF-defined sensitivity: 66.3%; specificity: 54.7%) and 1.61 mg/L (ATPIII-defined sensitivity: 67.4%; specificity 53.8%). Due to the wide range of variability of hs-CRP, even in an asymptomatic population, the specificity and sensitivity of the cut off points are relatively weak.

Overall, the American Heart Association/Centres for Disease Control recognized that individuals with a hs-CRP> 3g/L are a high-risk group for CVD. [18] Among our sample population, 29.2% of subjects were found to have hs-CRP>3 mg/L. It has been reported that 25% of the middle-aged population in the United States has serum levels of CRP> 3 mg/L; [19] this was approximately 18% in a Chinese population. [20] It therefore appears that the percentage of patients with levels of hs-CRP above the threshold for increased risk of CVD, is high in the Persian population.

We found that women in our population sample had higher levels of serum hs-CRP than the men, and this is consistent with previous publications[21,22] . The percentage of women increased in each quartile for serum hs-CRP, with the 4th quartile containing approximately 80% females. . Whether there is a gender-specific effect of hs-CRP as a risk predictor of CVDs is still subject of debate, although some studies have reported that serum hs-CRP appeared to be considerably stronger marker of CV risk in women compared to men. [23] A strong relationship between serum hs-CRP and development of coronary spasm (an ischaemia-related phenomenon, angiographically-defined as a >70% methylergonovine-induced coronary artery spasm reduction in luminal diameter) was found predominantly in women. [24]

We found an independent effect of smoking on serum hs-CRP concentrations. The prevalence of current smokers was significantly higher in the 4th quartile of hs-CRP. While results of previous studies have been conflicting, smoking habit appears to be associated with increased serum hs-CRP.[25,26].

In conclusion we found a significant relationship between serum hs-CRP and the presence of MetS and current smoking habit in a large Iranian cohort of subjects without a baseline history of CVD. In this population serum hs-CRP was particularly high in women. As the MASHAD study is a prospective, longitudinal cohort **there will be opportunity** to quantify the predictive of value of baseline hs-CRP concentration on cardiovascular outcome.

Table1. Demographic and biochemical characteristics of individuals in quartiles of hs-CRP

	1st quartile (N=2446) 0.72 (0.59-0.85) mg/l	2nd quartile (N=2463) 1.30 (1.14-1.4) mg/l	3rd quartile (N=2427) 2.29 (1.92-2.81) mg/l	4th quartile (N=2442) 6.63 (4.61-11.95) mg/l
Age(y)	46.9±8.2	47.6±8.2	48.7±8.1	49.0±8.3***
Gender (male) (%)	1149 (47.0%)	1058 (43.0%)	890 (36.7%)	814 (33.3%)***
Systolic blood pressure (mmHg)	118.6±18.6	121.1±17.8	122.8±18.5	124.9±20.9***
Diastolic blood pressure (mmHg)	77.5±12.0	78.9±12.3	79.9±11.1	80.4±11.5***
Fasting blood glucose (mmol/L)	4.7±1.6	5.0±1.9	5.3±2.2	5.7±2.7***
Total cholesterol (mmol/L)	4.7±0.9	4.9±1.0	5.1±1.1	5.2±1.2***
Triglyceride (mmol/L)	1.2 (0.8)	1.3(0.9)	1.4 (1.0)	1.5(0.9)***
LDL-C (mmol/L)	2.8±0.8	2.9±0.9	3.1±1.0	3.2±1.0***
HDL-C (mmol/L)	1.0±0.3	1.1±0.3	1.1±0.2	1.1±0.3***
Body mass index (kg/m^2)	26.0±4.1	27.2±4.3	28.7±4.4	29.8±5.2***
Waist Circumference (cm)	90.7±10.9	94.7±11.1	96.9±11.7	98.6±12.8***
Diabetes mellitus (%)	204 (8.4%)	285 (11.7%)	385 (16.1%)	500 (20.9%)***
Hypertension (%)	558(23.0%)	724 (29.8%)	837(35.0%)	932 (38.8%)***
Current smoking (%)	475 (19.4%)	544 (22.1%)	534 (22.0%)	545 (22.3%)**
Metabolic syndrome - IDF(%)	634 (25.9%)	862 (35%)	1085 (44.7%)	1220 (50.0%)***
Metabolic syndrome-ATP III	506(21.0%)	721(29.5%)	975(40.5%)	1115(45.9%)***

Values expressed as mean ± SD for variables with normal distribution, and median and interquartile rang for non-normally distributed data. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. *p<0.01, **p<0.05,***p<0.001

Table 2. The relative risk of being within 2nd , 3rd and 4th quartile of hs-CRP associated with risk factors and metabolic syndrome

	Reference group and second quartile	Reference group and third quartile	Reference group and forth quartile
Age (y)	1.002 (0.99-1.01)	1.02 (1.01-1.03)***	1.02 (1.01-1.03)***
Sex (male)	0.99 (0.87-1.13)	0.86 (0.76-0.97)*	0.85 (0.75-0.96)**
BMI (kg/m^2)	1.06 (1.04-1.07)***	1.13 (1.11-1.14)***	1.18 (1.16-1.20)***
LDL(mmol/L)	0.996 (0.993-1.00)*	0.99 (0.98-1.00)***	0.99 (0.98-1.00)***
Total cholesterol (mmol/L)	1.01 (1.00-1.01)***	1.01 (1.01-1.02)***	1.02 (1.01-1.03)***
Current smoking	1.29 (1.22-1.49)***	1.40 (1.21-1.62)***	1.47 (1.26-1.70)***
Metabolic syndrome-IDF	1.18 (1.03-1.35)*	1.32 (1.15-1.51)***	1.35 (1.18-1.55)***
Metabolic syndrome-ATP III	1.20 (1.05-1.35)*	1.35 (1.17-1.51)***	1.40 (1.18-1.50)***

Adjusted odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests. BMI, body mass index; *p<0.01, **p<0.05; ***p<0.001

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