



Metabolic Syndrome and Inflammatory Biomarkers in Adults: A Population-Based Survey in Western Region of Iran

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ABSTRACT

Background: There is evidence that inflammation may be involved in pathogenesis of MetS. Inflammatory biomarkers are moving to the forefront as the potent predictors of MetS.

Objectives: The present study aimed to evaluate the association between MetS and some inflammatory biomarkers.

Patients and Methods: This community-based cross-sectional study was conducted on 800 subjects aged above 35 years selected through random sampling in Borujerd (west of Iran) from 2011 to 2013. MetS was defined based on ATP III criteria and the subjects were divided into two groups (MetS and non-MetS groups). Waist circumference and Body Mass Index (BMI) were calculated. In addition, blood samples were taken and C-Reactive Protein (CRP), lipid profile, Fasting Blood Sugar (FBS), and Bleeding Time (BT) were measured. Then, the correlations between MetS and the above-mentioned variables were estimated. After all, the data were entered into the SPSS statistical software (v. 17) and analyzed using T-test, chi-square, median test, and spearman's rank correlation.

Results: In this study, 344 subjects (43%) met the ATP III criteria. The results showed a significant difference between MetS and non-MetS groups regarding BMI, white blood cell, total cholesterol, LDL, platelet, and high-sensitivity CPR (hs-CRP) ($P < 0.0001$, $P = 0.040$, $P < 0.0001$, $P < 0.0001$, and $P = 0.045$, respectively). Besides, waist circumference, Triglyceride (TG), FBS, and systolic and diastolic blood pressure were significantly higher, while HDL was significantly lower in the MetS group ($P < 0.0001$).

Conclusions: The incidence rate of MetS in our survey was higher compared to the previous reports. In addition, this incidence rate was higher in females in comparison to males. The results also showed a significant correlation between inflammatory biomarkers and MetS and that the higher levels of hs-CRP were associated with higher rate of MetS.

► Implication for health policy/practice/research/medical education:

Given the paucity of current research regarding the associations between inflammatory markers and metabolic risk factors in Lor population, this study investigated the relationships between cardiometabolic risk factors and metabolic syndrome in an adult population in Borujerd, western region of Iran.

1. Background

Metabolic Syndrome (MetS), also known as syndrome X,

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is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function (1). World Health Organization (WHO), the National Cholesterol Education Program—Adult Treatment Panel III (NCEP ATP III), and the International Diabetes Federation (IDF) have

recognized MetS as a major risk factor for both type 2 Diabetes Mellitus (DM) and Cardiovascular Diseases (CVD) (2). The prevalence rate of MetS was reported to be about 20 - 30% in developed countries (3, 4) and about 33.7% in Iran, which is one of the highest incidence rates worldwide (5). There is also evidence that chronic inflammation may induce insulin resistance. Low-grade inflammation has been hypothesized to be involved in the pathogenesis of MetS (6). This pro-inflammatory status may lead to clinical and biochemical manifestations of MetS (7). Previous studies have evaluated the association between MetS and some inflammatory biomarkers, and have come to conflicting conclusions (6-9). Moreover, other studies have indicated associations between elevated mean C-Reactive Protein (CRP) concentrations, a sensitive marker of subclinical inflammation, and insulin resistance and components of MetS (9-11). Inflammatory biomarkers are considered to be amongst the most potent predictors of MetS, one of the most serious health concerns both in Iran and around the world.

2. Objectives

Given the paucity of the current research regarding the associations between these markers and metabolic risk factors in Lur ethnic group, the present study aims to investigate the relationships between cardiometabolic risk factors and MetS in an adult population in Borujerd, western region of Iran.

3. Patients and Methods

3.1. Study Design and Subjects

The present community-based cross-sectional study was a large part of the Borujerd Health and Nutrition Survey (BHNS) conducted by Lorestan University of Medical Sciences from 2011 to 2013. BHNS was a community-based descriptive program that was performed to evaluate the medical history and health-related lifestyle factors of Lur ethnic group in Borujerd, Lorestan (west of Iran). In this study, 25 clusters of subjects over 35 years old from urban (16 clusters) and rural (9 clusters) areas of Borujerd, Lorestan were selected over a period of 2 years (June 2011 to June 2013).

The exclusion criteria of the study were off-site examination, fasting plasma glucose ≥ 126 mg/dL or use of insulin or oral hypoglycemic agents, having a history of angina pectoris, coronary insufficiency, myocardial infarction, heart failure, transient ischemic attack, stroke, or intermittent claudication (determined by a panel of three physicians), and missing information regarding MetS traits or insulin treatment.

Initially, the included patients were fully examined and questioned about their demographic information (sex, age, and residential area (urban/rural)), diet, physical activity, tobacco use, history of any possible diseases, and drug consumption. In addition, current smokers were defined by self-report of cigarette smoking during the year prior to the study. After diagnosis of MetS, the subjects were divided into two groups (MetS and non-MetS groups).

3.2. Anthropometric and Blood Pressure Measurements

Waist Circumference was measured at the minimum

circumference between the iliac crest and the rib cage over light clothing using a flexible measuring tape without any pressure to the body surface being recorded to the nearest 0.1 cm. To avoid subjective error, all measurements were performed by the same male physician for all the males and by the same female physician for all the females.

Height (by a stadiometer using a centimeter scale) and weight (by a clinical scale) were measured in light clothing and without shoes. Besides, Body Mass Index (BMI) was calculated by body weight (kg) / height (m²), and BMI ≥ 30 kg/m² was defined as obesity.

Blood pressure was measured twice after a 5-min rest from the right hand in a seated position using a standard mercury manometer by certified technicians, and the mean was recorded as blood pressure. Hypertension was defined as Systolic Blood Pressure (SBP) ≥ 140 mmHg, Diastolic Blood Pressure (DBP) ≥ 90 mmHg, or use of antihypertensive medications.

3.3. Laboratory Measurements

Blood samples were drawn after 10 - 12 hours of fasting through the antecubital vein. The samples were centrifuged within 30 - 45 min after collection. Fasting Blood Glucose (FBG), Triglycerides (TG), Total Cholesterol (TC), and Low and High Density Lipoprotein Cholesterol (LDL-C, HDL-C) were measured on fresh samples by standard kits (Pars Azmoun, Iran) using an auto-analyzer (Hitachi, Japan). Besides, Fasting Blood Sugar (FBS) was measured by enzymatic colorimetric method using glucose oxidase test. In addition, serum TG concentrations were assayed using commercially available enzymatic reagents with glycerol phosphate oxidase. Also, HDL-C was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid, and LDL was estimated using the Friedewald equation (12).

Complete Blood Count (CBC) indices were measured by a cell counter (Sysmex K-21, Japan).

Additionally, serum uric acid was measured by enzymatic colorimetry using an autoanalyzer (Selectra-2, Italy) and the relevant commercial kits (Pars Azmoun, Tehran, Iran). Finally, plasma high-sensitivity CRP (hs-CRP) concentration was measured using a latex-enhanced nephelometry (Behring BN II nephelometer, Dade-Behring Inc., Germany). The lower limit of detection of the assay was 0.02 mg/dL.

The subjects' Bleeding Time (BT) was determined according to the Ivy method. The normal range of BT in Borujerd was 2.80 - 2.95 minutes. Besides, the range of BT was 2.83 - 3.06 minutes in women and 2.70 - 2.90 minutes in men (13).

3.4. Definition of Metabolic Syndrome

In this study, MetS was defined based on the NCEP ATP III criteria; i.e., the presence of three or more of the following five symptoms (14):

- 1- Abdominal obesity: waist circumference > 102 cm in men and > 88 cm in women
- 2- Hypertriglyceridemia: serum TG level ≥ 150 mg/dL or drug treatment for elevated TG
- 3- Low HDL-cholesterol: < 40 mg/dL in men and < 50

mg/dL in women or drug treatment for low HDL-C

4- High blood pressure: SBP \geq 130 mmHg and/or DBP \geq 85 mmHg or drug treatment for elevated blood pressure

5- High fasting glucose (FBS): serum glucose level \geq 110 mg/dL or being under treatment for diabetes.

3.5. Statistical Analysis

All the data were analyzed by Statistical Package for Social Studies (SPSS), version 17 (SPSS Inc, Chicago, IL, USA). The continuous variables were reported as Mean \pm SD, while the categorical variables were presented as percentage. The means were compared using Student t-test, and the prevalence of MetS among males and females was determined and compared through Chi-square test. As the distribution of CRP level was skewed, the median values of CRP level were calculated and the groups were compared by median test. Besides, Spearman's rank correlation analysis was performed between CRP and each MetS component. $P < 0.05$ was considered as statistically significant.

3.6. Ethical Considerations

The study protocol was approved by the Ethics Committee of Lorestan University of Medical sciences. Moreover, all the respondents signed written informed consents and voluntarily participated in the study after the study objectives and procedures were explained to them.

4. Results

In this study, a total of 344 participants (43%) met the MetS criteria according to ATP III criteria. The participants' means of age, BMI, SBP, and DBP were 54.89 ± 12.11 years, 26.75 ± 4.92 kg/m², 127.24 ± 21.16 mmHg, and 79.48 ± 11.79 mmHg, respectively. Besides, their mean hs-CRP was 6.54 ± 8.26 mg/L. The components of MetS and the Spearman's rank correlation coefficients between hs-CRP and cardiometabolic risk factors have been presented in Table 1. The results showed a significant unadjusted positive correlation between hs-CRP and BMI, hypertension, waist circumference, cholesterol, and TG.

In addition, a negative correlation was found between hs-CRP and HDL. The participants' baseline characteristics and cardiometabolic risk factors have been compared in Table 2. Accordingly, a significant difference was observed between MetS and non-MetS groups with respect to BMI,

White Blood Cell (WBC), TC, LDL, platelet, and hs-CRP ($P < 0.0001$, $P = 0.040$, $P < 0.0001$, $P < 0.0001$, and $P = 0.045$, respectively). Furthermore, the overall prevalence of MetS was significantly higher among women (73.5%) compared to men (26.5%) ($P < 0.0001$).

Considering the MetS components according to ATP-III criteria (waist circumference, TG, HDL, FBS, SBP, and DBP), a statistically significant difference was found between MetS and non-MetS groups (Table 2); such a way that waist circumference, TG, FBS, SBP, and DBP were significantly higher, while HDL was significantly lower in the MetS group ($P < 0.0001$).

After hs-CRP concentration was coded as at least 3 mg/L versus less than 3 mg/L, the prevalence of MetS was significantly higher in the subjects whose hs-CRP was equal to or higher than 3 mg/L (50.1% vs. 42.5%, $P = 0.032$).

5. Discussion

The present cross-sectional study evaluated the associations between MetS and inflammatory biomarkers in 800 patients (52.4% females and 47.6% males) with a mean age of 54.89 years. According to ATP III criteria, the prevalence of MetS was 43% which was higher compared to other reports from Iran and other countries. In a report from Tehran Lipid and Glucose Study by Zabetian et al. (15), the prevalence of MetS was approximately 33.7%. Besides, Sharifi et al. (16) found the prevalence of MetS to be 23% in Zanjan Province, Iran. Additionally, a national Iranian survey of MetS in 2007 showed an age standardized prevalence of 34.7% based on ATP III criteria (17).

The present study findings indicated a significant relationship between inflammatory biomarkers and MetS. Moreover, a significant difference was found between the MetS and non-MetS group concerning all the MetS components, namely waist circumference, TG, HDL, FBS, SBP, and DBP. The two groups were also significantly different with regards to BMI, WBC, TC, LDL, platelet, and hs-CRP. Previous reports demonstrated associations between MetS and inflammatory biomarkers. These studies revealed that MetS could be characterized by a status of chronic subclinical inflammation. This condition has been suggested to play a role in the pathophysiology of cardiometabolic diseases (18). In this regard, Tamakoshi et al. (19) indicated that a variety of MetS components were

Table 1. Spearman's Rank Correlation Coefficients between hs-CRP and MetS Components and Other Cardiometabolic Risk Factors

Characteristic	R	P value
Age	0.34	0.341
BMI	0.21*	0.032
Hypertension	0.24*	0.047
Waist circumference	0.82*	0.021
Total cholesterol	0.41*	0.019
Triglyceride	0.11*	0.004
LDL	0.49*	0.028
HDL	-0.33*	0.002
Fasting blood glucose	0.67	0.059
Bleeding time	0.27	0.489
Uric acid	0.49	0.172

*Correlation is significant at 0.05 level

Table 2. Comparison of Baseline Characteristics and Cardiometabolic Risk Factors between MetS and Non-MetS Groups

Characteristic	Metabolic Syndrome		P value
	Yes (n = 344)	No (n = 456)	
Age (years)	55.51 ± 10.88	54.37 ± 13.09	0.195*
BMI (kg/m ²)	28.98 ± 4.79	25.06 ± 4.29	< 0.0001*
Gender (%)			
Males	91 (26.5)	290 (63.6)	< 0.0001**
Females	253 (73.5)	166 (36.4)	
Systolic blood pressure (mmHg)	136.26 ± 20.16	119.87 ± 18.65	< 0.0001*
Diastolic blood pressure (mmHg)	83.51 ± 12.06	76.16 ± 10.68	< 0.0001*
Waist circumference (cm)	98.26 ± 10.14	87.73 ± 10.94	< 0.0001*
Total cholesterol (mg/dL)	211.52 ± 38.98	178.35 ± 35.81	< 0.0001*
Triglyceride (mg/dL)	221.94 ± 134.67	117.07 ± 60.36	< 0.0001*
LDL (mg/dL)	126.31 ± 41.17	107.83 ± 35.41	< 0.0001*
HDL (mg/dL)	40.46 ± 5.73	46.73 ± 6.69	< 0.0001*
Fasting blood glucose (mg/dL)	123.59 ± 53.12	102.09 ± 26.23	< 0.0001*
Bleeding time (sec)	55.51 ± 10.88	54.37 ± 13.09	0.112*
Uric acid (mg/dL)	7.11 ± 4.72	6.84 ± 2.74	0.073*
Hemoglobin (g/dL)	13.01 ± 1.32	13.05 ± 1.47	0.673*
WBC (cell/ μ L)	6.35 ± 1.64	6.09 ± 1.89	0.040*
Hematocrit (%)	38.98 ± 4.22	38.96 ± 4.43	0.936*
Platelet (cell/L)	248.47 ± 66.81	232.26 ± 63.23	< 0.0001*
hs-CRP (mg/L)	6.96 ± 8.79	6.16 ± 7.74	0.045***

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein cholesterol; WBC, white blood cell; hsCRP, high-sensitivity C-reactive protein

*T-test Statistics, ** chi-square Statistics, *** median test Statistics

associated with elevated CRP levels in a systemic low-grade inflammatory state. Moreover, another report by Dallmeier et al. (8) signified that MetS was associated with multiple inflammatory biomarkers. The authors also designated that the association between inflammation and MetS was largely accounted by MetS components.

A study conducted in Japan showed that the components of MetS, such as obesity, hypertriglyceridemia, hyper-LDL-cholesterolemia, diabetes, hyperinsulinemia, and hyperuricemia, were significantly associated with elevated CRP levels (19). Similar to the study by Tamakoshi et al., several other reports are also in agreement with our findings regarding the relationship between BMI and inflammation (20-24).

The current study results indicated a significant relationship between MetS and TC, HDL, and LDL. In the same line, other studies showed that inflammatory biomarkers, such as cytokines, led to dyslipidemia with increased Very-Low Density Lipoproteins (VLDL) and deactivated Liver X Receptors (LXRs) that increased cholesterol accumulation and subsequently elevated LDL-C (23, 25).

Earlier reports suggested that inflammatory cytokines down regulated major anabolic cascades involved in insulin signaling and activated insulin resistance in liver, adipose tissue, and skeletal muscle, disturbing whole body insulin sensitivity, which eventually led to impaired glucose homeostasis (18). Although CRP appears to be predominantly produced in the liver, previous investigators showed increased CRP gene expression from adipose tissue and vascular endothelium, a component of the stromal vascular fraction (26). The mechanisms underlying these associations are not clearly elucidated, but there are possible explanations.

During the development of MetS, there is an increase in white adipose tissue caused by an adipocyte hypertrophy/hyperplasia, an increased infiltration of immune cells, and an imbalance between production of pro-inflammatory and anti-inflammatory adipokines. The presence of the macrophages infiltration in adipose tissue makes it a source of inflammatory signals release that acts in the adipose tissue metabolism itself and controls metabolic changes associated with obesity (27). Therefore, MetS is a pro-inflammatory state and the adipose tissue of MetS contributes to the increased inflammation of these patients (26).

The present study was an uncontrolled research, limiting the generalizability of the results. Thus, further controlled investigations with longer follow-ups and larger series are recommended to validate the findings reported here.

The incidence rate of MetS in our survey was higher compared to the previous reports. Also, this incidence rate was higher among females in comparison to males. Moreover, the results showed a significant correlation between the inflammatory biomarkers and MetS, and that higher levels of hs-CRP were associated with higher incidence rates of MetS.

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Authors' Contribution

Ali Maleki, Negin Rashid, Hamidreza Aghaei, and Mahdi Montazeri provided conception and design of the study

and revised the article critically for important intellectual content, Mohammad Montazeri, Reza Ghanati and Saeid Foroughi participated in data acquisition, drafting the manuscript, and data analysis and interpretation, Farshid Alyari and Farid Falsafi revised the manuscript critically for important intellectual content and participated in data acquisition and data analysis.

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