Evaluation of heart rate reserve and high-sensitivity C-reactive protein in individuals with and without metabolic syndrome in Isfahan, Iran

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Abstract

BACKGROUND: Lack of heart rate increase proportionate to exercise causes poor prognosis. Moreover, inflammatory factors such as C-reactive protein (CRP) are associated with atherosclerosis. The current study compared these two indices in individuals with and without metabolic syndrome in Isfahan, Iran.

METHODS: This study was performed on 203 people without and 123 patients with metabolic syndrome who were randomly selected from the participants of the Isfahan Cohort Study. The demographic data, waist circumference, blood pressure, height, and weight of the participants were recorded. Moreover, serum tr`iglyceride (TG), fasting blood sugar (FBS), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and high-sensitivity CRP (hs-CRP) levels were measured. Exercise test was carried out according to the Bruce standard protocol and heart rate reserve (HRR) was determined and recorded. The age-adjusted data was analyzed using generalized linear regression and student's t-test in $SPSS_{15}$.

RESULTS: The mean ages of participants without and with metabolic syndrome were 54.16 ± 8.61 and 54.29 ± 7.6 years, respectively. The corresponding values for mean LDL levels were 116.17 ± 24.04 and 120.12 ± 29.55 mg/dl. TG levels were 140.38 ± 61.65 and 259.99 ± 184.49 mg/dl for subjects without and with the metabolic syndrome, respectively. The mean FBS levels were 81.81 ± 9.90 mg/dl in the participants without the syndrome and 107.13 ± 48.46 mg/dl in those with metabolic syndrome. The mean systolic blood pressure was 116.06 ± 13.69 mmHg in persons without metabolic syndrome and 130.73 ± 15.15 mmHg in patients with the syndrome. The values for mean diastolic levels in the two groups were 76.52 ± 6.69 and 82.84 ± 8.7 mmHg, respectively. While the two groups were not significantly different in terms of HRR (P = 0.27), hs-CRP levels in the metabolic syndrome group was significantly higher than the other group (P = 0.02).

CONCLUSION: We failed to establish a relationship between HRR and the metabolic syndrome. However, the observed relationship between metabolic syndrome and hs-CRP level, which is an inflammatory factor, indicates elevated levels of hs-CRP in patients with metabolic syndrome.

Keywords: Metabolic Syndrome, Exercise Test, Heart Rate Reserve, High-Sensitivity C-Reactive Protein.

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Introduction

In 1988, Reaven introduced metabolic syndrome as a set of risk factors, basically including insulin resistance, hypertension (HTN), dyslipidemia, and other metabolic disorders, which increase the risk of cardiovascular diseases.[1] Therefore, scientists all around the world focused on identification of the syndrome to prevent, treat, and lower the risk of cardiovascular diseases.[2,3] In patients with metabolic syndrome, exercise test is helpful in early diagnosis of cardiovascular diseases and also prediction of the risk of mortality and occurrence of cardiovascular events.[4-6] Exercise test is an affordable, low-risk method which provides valuable information for physicians. Heart rate reserve (HRR) is one of the important findings of the exercise test. HRR is defined as increased heart rate as a result of increased activity. HRR values lower than or equal to 85% are considered to be normal and desirable and thus associated with poor prognosis.[7-16]

High-sensitivity C-reactive protein (hs-CRP) is an inflammatory factor, known to be related to the

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metabolic syndrome.[17-23] However, all patients with metabolic syndrome are not at the same risk for development of cardiovascular diseases, and several factors including race, lifestyle, and health culture are effective in this respect.[24,25] Various studies have demonstrated different results regarding these factors. Furthermore, the effectiveness of various interventional approaches in reducing the disease risk is not identical.[26-29] As mentioned, the metabolic syndrome has been suggested to play an important role in development of cardiovascular diseases which are in turn a major cause of death among adults in Iran. Moreover, the prevalence of metabolic syndrome is very high in Iranian population which differs ethically and climatically with other populations studied in other countries.[30-33] Therefore, in the current study, we compared the HRR and hs-CRP of patients with and without metabolic syndrome.

Materials and Methods

This cross-sectional study was carried out on 203 individuals without metabolic syndrome and 123 individuals with metabolic syndrome who were registered in the Isfahan Cohort Study. As a prospective cohort study, the Isfahan Cohort Study started in 2002 and will continue until the end of 2012. It used multistage cluster sampling to select people older than 34 years of age from Isfahan, Najafabad, and Arak (3 cities in central Iran). All the demographic and behavioral data, as well as the indices such as blood pressure, body mass index (BMI), and the results of routine blood tests were recorded for all participants in the first year of the study. Afterwards, the occurrence of cardiac infarction, stroke, sudden death, and hospitalization were asked via telephone calls with two-year intervals. The clinical examinations and routine blood tests were reperformed in the fifth and sixth years of the follow-up. Further details were published by Sarraf-Zadegan et al. in 2003.[30]

The current study used accessible sampling to select 260 individuals with metabolic syndrome and 260 individuals without metabolic syndrome from the participants of the Isfahan Cohort Study. Using the provided telephone numbers in the records of participants, the individuals were invited to take part in the study. Finally, 123 individuals with metabolic syndrome and 203 individuals without the syndrome participated in all steps of the study. They were invited to the Isfahan Cardiovascular Research Center (Isfahan, Iran) at an appropriate time based on their schedule. They then attended interviews and the objectives and methodology of the study were explained for them. After signing a written consent, they were included in the study. The metabolic syndrome was approved according to the protocol of the National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATPIII). Therefore, individuals having three or more of the following criteria were considered to have the metabolic syndrome:

1- waist circumference above 102 cm in men and above 88 cm in women;

2- blood triglyceride (TG) level ≥ 150 mg/dl;

3- fasting blood sugar (FBS) ≥ 110 mg/dl;

4- high density lipoprotein (HDL) level ≤ 40 mg/dl in men and ≤ 50 mg/dl in women; and

5- systolic blood pressure (SBP) ≥ 135 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg.[34]

The members of the control group were individuals without metabolic syndrome who were selected from the same population in the Isfahan Cohort Study. They were included after matching for gender and age. The exclusion criteria were not being able to perform the exercise test, the presence of an absolute contraindication for performing exercise test, for instance myocardial infarction in the recent two days, advanced heart block, acute pulmonary emboli, uncontrolled HTN, acute myocarditis, severe aortic valve stenosis, or uncompensated cardiac failure, pregnancy, and not being willing to participate.[4] The participants referred to the Isfahan Cardiovascular Research Center for the examinations after 12 hours of fasting. General physical examination and blood sampling were followed by waist circumference, blood pressure, weight, and height measurements according to international standards.[35] TG and total cholesterol (TC) levels were determined using the enzymatic method by an autoanalyzer (Hitachi 902). After evaluating HDL levels using heparin-magnesium precipitation,[36] LDL levels were calculated according to Friedewald formula.[37] If the TG level was above 400 mg/dl, the LDL level was directly measured using a specific kit. The fasting blood sugar (FBS) level was determined using an enzymatic method (glucose oxidase). The 12-lead electrocardiogram (ECG) was taken by a trained technician according to the World Health Organization's multinational monitoring of trends and determinants in cardiovascular disease (WHO MONICA).[38] Exercise test was then carried out according to Bruce or modified Bruce protocol and the HRR value was determined and recorded in each participant's file. The level of hs-CRP was quantitatively determined using specific kits. Since the values were expressed as ≥ zero, we considered levels of 0-6 mg/l as negative and above 40 mg/l as +3.

The data obtained was adjusted for age and then analyzed by generalized linear regression and student's t-test in $SPSS_{15}$ (SPSS Inc., Chicago, IL, USA). P values below 0.05 were considered to be statistically significant.

In addition, hypercholesterolemia, hypertriglyceridemia, diabetes, and HTN were defined as TC > 200 mg/dl while using cholesterol lowering agents, TG > 200 mg/dl while using TG lowering agents, FBS > 126 mg/dl despite taking anti-diabetic drugs, and SBP > 140 mmHg or DBP > 90 mmHg while taking at least one anti-hypertensive drug, respectively.[24]

Results

Among the 326 individuals who participated in this study, 56 men and 67 women had metabolic syndrome while 122 men and 81 women did not suffer from the syndrome. The youngest and oldest participants aged 35 and 82 years, respectively. The mean ages of subjects with and without metabolic syndrome were 54.29 ± 7.6 and 54.16 ± 8.61 years, respectively.

The values obtained in the examinations for weight, waist circumference, SBP, DBP, and the laboratory findings stratified by gender and the presence of metabolic syndrome were adjusted by age and provided in table 1. As the table shows, there was a statistically significant relationship between metabolic syndrome and the values of waist circumference, weight, TG, TC, HDL, FBS, SBP, and DBP (P < 0.001). The frequency rates of dyslipidemia, diabetes, and HTN in the group with metabolic syndrome were higher than those in the group without metabolic syndrome (Table 2).

According to the indices of the exercise test, the HRR values in the group without metabolic syndrome were 75.09% and 73.17% in men and women, respectively. On the other hand, the values in the group with metabolic syndrome were 73.52% and 73.13%, respectively. The two groups were not significantly different in this respect (P = 0.27) (Table 3).

Table 1. Comparison of biochemical and clinical indices in individuals with and without metabolic syndrome

	Without metabolic syndrome	With metabolic syndrome	P
Age (years)	54.16 ± 8.62	54.29±7.60	0.890
Waist circumference (cm)	87.97 ± 9.43	98.42 ± 8.74	< 0.001
Weight (Kg)	70.10 ± 11.08	80.35 ± 12.85	< 0.001
Triglyceride (mg/dl)	140.38 ± 61.66	259.99 ± 184.50	< 0.001
Total cholesterol (mg/dl)	201.17 ± 35.79	217.34 ± 49.60	0.003
High density lipoprotein (mg/dl)	47.91 ± 11.62	41.77 ± 8.67	< 0.001
Low density lipoprotein (mg/dl)	116.17 ± 24.05	120.12 ± 29.55	0.21
Fasting blood sugar (mg/dl)	81.81 ± 9.90	107.13 ± 48.46	< 0.001
Systolic blood pressure (mmHg)	116.06 ± 13.70	130.74 ± 15.16	< 0.001
Diastolic blood pressure (mmHg)	76.53 ± 6.70	82.84 ± 8.70	< 0.001

Values are expressed as mean ± SD.

Table 2. Relative frequency of diabetes, dyslipidemia, and hypertension based on gender and the presence of metabolic syndrome

	Men			Women		
	With metabolic syndrome	Without metabolic syndrome	P	With metabolic syndrome	Without metabolic syndrome	P
Dyslipidemia	91.10%	63.90%	< 0.001	89.60%	63%	< 0.001
Diabetes	32.10%	1.60%	< 0.001	28.40	1.20%	< 0.001
Hypertension	50%	9%	< 0.001	32.80%	11.10%	< 0.001

Table 3. Heart rate reserve in the groups with and without metabolic syndrome

	Heart rate reserve
Men without metabolic syndrome	70.09% ± 7.571%
Women without metabolic syndrome	73.17% ± 7.601
P	0.079
Men with metabolic syndrome	73.52% ± 7.685%
Women with metabolic syndrome	73.13% ± 9.21%
P	0.805
P between the two groups	0.270
Individuals with metabolic syndrome	73.31% ± 8.522%
Individuals without metabolic syndrome	74.33% ± 7.622%

Table 4. High-sensitivity C-reactive protein (hs-CRP) levels in the groups with and without metabolic syndrome

Hs-CRP	Individuals with metabolic syndrome	Individuals without metabolic syndrome	P
Mean ± SD	18.74 ± 26.37	9.03 ± 14.94	
Median	7	4	0.019
Interquartile range	4-15	1.2-7	

The mean hs-CRP levels in the groups with and without metabolic syndrome were significantly different (26.37 ± 18.74 vs. 14.94 ± 9.03 mg/l; P = 0.019) (Table 4).

Discussion

In the current study, we evaluated two important factors, i.e. HRR and hs-CRP, for predicting the risk of cardiovascular diseases in individuals with and without metabolic syndrome who attended the Isfahan Cohort Study. HRR values were not significantly different between the two groups and the two sexes. However, the hs-CRP level was significantly higher in metabolic syndrome group. Similarly, Regitz-Zagrosek stated that the impact of gender differences on the prognosis of metabolic syndrome was not definitely confirmed.[39] Moreover, the impact of gender differences on HRR in normal people is not definitely defined.[39] On the contrary, Nilsson et al. stated that HRR is lower only in women with metabolic syndrome.[40]

In a study, it was shown that the increase in the hs-CRP level in obese individuals was 4.6 folds more than non-obese people. It was detected that the mean log of hs-CRP elevated progressively as the components of metabolic syndrome increased. Hs-CRP level was also reported to be evidently higher in individuals having three or more components of the syndrome compared with those having one component of the syndrome.[17] Another study however, suggested that only abdominal obesity was associated with significant increase in hs-CRP levels.[18]

Investigations on the relationship between inflammation and metabolic syndrome revealed that individuals with the syndrome had a significantly higher level of hs-CRP in comparison with individuals without the syndrome. Several factors may contribute to increased levels of hs-CRP in the metabolic syndrome. One of these factors could be the effect of adipocytes, tumor necrosis factor (TNF), interleukin 6 (IL-6), and adiponectin on the hs-CRP level in obese people.[19] Statistically significant relationships have also been reported between obesity and inflammatory markers.[20] A previous study demonstrated higher levels of visceral obesity to be associated with elevated levels of CRP, TNF, and IL-6.[21] Furthermore, increased levels of CRP have been found to be related with insulin resistance and the metabolic syndrome.[22] Moreover, a study on American women reported higher CRP levels in women with one component of the syndrome compared to those without any components.[23]

In the current study, the mean level of hs-CRP in the group with metabolic syndrome was significantly higher than that in the group without the syndrome (P = 0.019). This finding is in agreement with the results reported in other studies.

Therefore, the results of this study suggested that compared to HRR, hs-CRP level had a more powerful relationship with metabolic syndrome in our studied population. Such a finding would be helpful for physicians and health planners in making more accurate decisions. Moreover, this study could serve as a foundation for further studies in our community on people with metabolic syndrome, the relationship between the syndrome and cardiovascular diseases, and also the predictive values of the above-mentioned indices.

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Conflict of Interests

Authors have no conflict of interests.

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