Carotid intima-media thickness and plasma fibrinogen among subjects with metabolic syndrome: Isfahan cohort study, Iran

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Original Article

Abstract

BACKGROUND: The role of plasma fibrinogen, a key regulator of inflammation processes and increased carotid intima-media thickness (cIMT) to predict metabolic syndrome (MetS) is currently under investigation. We assessed differences in the indicators of cIMT and also plasma fibrinogen level between MetS and non-MetS subjects. We also assessed the role of these two parameters for independently relationship with MetS state.

METHODS: The subjects in this cross-sectional survey were population-based samples of 93 men and women aged ≥ 35 years and over who were selected from the Isfahan cohort study, Isfahan, Iran. Fibrinogen was measured by the clotting assay of Clauss. Ultrasound studies of the carotid artery were performed to measure cIMT. MetS defined based on the National Cholesterol Education Program's Adult Treatment Panel III.

RESULTS: The mean level of plasma fibrinogen was not different in the two groups with and without MetS (240.10 ± 27.80 vs. 242.56 ± 35.82, P = 0.714), but the mean of cIMT was considerably higher in MetS group than in non-MetS group (0.85 ± 0.06 mm vs. 0.66 ± 0.09 mm, P < 0.001). Using a multivariable logistic regression model, high cIMT could effectively predict MetS state with the presence of different components of MetS (odds ratio = 17.544, 95% confidence interval = 2.151-142.860, P = 0.008). The optimal cutoff point of cIMT for discriminating these two clinical states was 0.6 mm yielding a sensitivity of 61.5% and a specificity of 59.6%.

CONCLUSION: Individuals with MetS demonstrated increased cIMT values compared with those without MetS. However, high plasma fibrinogen level may not be associated with MetS state.

Keywords: Metabolic Syndrome, Carotid Intima-Media Thickness, Fibrinogen, Prediction

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Introduction

Subclinical atherosclerosis in great vessels is one of the clear identified results of cardio-metabolic abnormalities like metabolic syndrome (MetS). One of the most important atherosclerotic-mediated changes is increased carotid intima-media thickness (cIMT) and hence has been agreed as a well-established surrogate index of coronary and cerebral atherosclerotic events.[1] According to recent evidences, this vascular event can be shown following appearance of MetS and its progression may be also prevented by spontaneous recovery from this syndrome.[2] Even, it has been indicated that MetS is more predictive of cIMT than the sum of the individual components of the syndrome.[3,4] However, while there are some reports that increased cIMT may not be associated with each of MetS components such as insulin resistance.[5] In this

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regard, evidences on associations between MetS and atherosclerosis as well as increased cIMT are eagerly waited for.

The role of plasma fibrinogen, a key regulator of inflammation processes, as a cardiovascular risk factor remains controversial. Some surveys could demonstrate that higher plasma fibrinogen concentrations were associated with a greater incidence of coronary heart disease and its progression.[6-10] Besides, increased age-adjusted plasma level of fibrinogen has been revealed to be associated with a cluster of cardiovascular risk factors and MetS components including obesity, high blood pressure, and dyslipidemia.[11] It is evidenced that some major components of MetS such as central obesity may be linked to elevation in plasma fibrinogen concentration through the mediation of blood pressure, C-reactive protein, as well as via being affected by cigarette smoking.[12] In this context, considering hyperfibrinogenemia as a main component of MetS has been recently recommended.

In the present study, we followed two targets: first, we assessed differences in the indicators of cIMT and also plasma fibrinogen level between MetS and non-MetS subjects. Second, we assessed the role of these two parameters for independently predicting MetS state.

Materials and Methods

The subjects in this cross-sectional survey were population-based samples of 93 men and women aged ≥ 35 years and over (power of study: 80%, α = 5%) who were selected by random sampling from the Isfahan, Iran, cohort study that was performed in 2001 in three central provinces in Iran, including Isfahan, Arak, and Najafabad and enrolled 6504 participants with the aim of detecting the incidence of cardiovascular diseases and its-related major risk factors.[13] The subjects with a history of any cardiovascular or related disorders, pregnant women, breastfeeding mothers, and those subjects with serious systemic illnesses from the study. The protocol of this study was approved by the Research and Ethics Committees of the Isfahan Cardiovascular Research Institute. The individuals enrolled in this study were informed about the aims of the investigation and those who agreed signed informed consent forms. All participants were asked to fast for 8-12 h before attending the first visit in order to obtain demographics information, medical history, to conduct clinical examination and venous blood samples for lab tests. In this regard, venous blood samples were drawn in vacuum tubes containing sodium citrate as an anticoagulant. Blood samples were centrifuged at 2500 rpm for 10 min to obtain plasma. The plasma was separated and stored at −70 °C for 2 weeks until the measurement. Fibrinogen was measured by the clotting assay of Clauss,[14] using a commercially available kit in the same laboratory. Serum total cholesterol was measured by enzymatic methods, and high-density lipoprotein (HDL) cholesterol was measured after heparin-manganese precipitation using the Liebermann–Burchard method using an autoanalyzer (Eppendorf, Hamburg, Germany). Hypercholesterolemia was defined as total cholesterol 240 mg/dl, HDL-cholesterol < 40 mg/dl in men, and < 50 mg/dl in women, triglycerides ≥ 240 mg/dl.[15] Serum glucose was measured by enzymatic methods. Diabetes mellitus was defined as serum glucose of 140 mg/dl or more fasting and/or blood glucose of 200 mg/dl or more non-fasting and/or taking hypoglycemic medication.[15] Measurement of blood pressure and anthropometric parameters were carried out following standard protocols.[16,17] Height in stocking feet and weight in light clothing were measured, and body mass index was calculated as weight (kg)/height (m^2) using Seca Stadiometer (Germany, 2009). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Hypertension was defined as SBP of 140 mmHg or more and/or DBP of 90 mmHg or more and/or taking antihypertensive medication.[15] MetS was defined based on the presence of three or more components of the defined criteria for MetS by the amended National Cholesterol Education Program's Adult Treatment Panel III (ATP-III).[16] The ATP-III criteria include: (1) fasting triglycerides > 150 mg/dl or lipid medications; (2) SBP > 130 mmHg, DBP > 85 mmHg, or use of antihypertensive medications; (3) fasting plasma glucose > 110 mg/dl or use of diabetes medications; (4) HDL cholesterol < 40 mg/dl (men) or < 50 mg/dl (women); and (5) waist circumference > 102 cm (men) or > 88 cm (women). Using the previous criteria we found 39 patients who were diagnosed to have MetS and 54 patients without MetS. Ultrasound studies of the carotid artery were performed to measure cIMT from the posterior wall of the left common carotid artery about 10 mm proximal from the bifurcation.[17] Incident high cIMT or plaque was defined as those with cIMT ≥ 90th percentile[18] that was estimated 0.75 in the present study by one observation.

Shapiro–Wilk and Kolmogorov–Smirnov test was used to check the normality of data distribution. Bartlett's test was used to check the homogeneity of variances. Differences in sex-specific mean values and proportions of baseline characteristics were compared between people who developed MetS and those who remained free of MetS by using a t-test or chi-square test. Logistic regression models were used to examine the relations of plasma fibrinogen and cIMT with the incidence of MetS. Correlation between the quantitative variables was tested by the Pearson's test. A receiver operating characteristic (ROC) curve was used to identify the best cutoff point of both fibrinogen and cIMT values by which to maximize the sensitivity and specificity of discriminating MetS from non-MetS conditions. For the statistical analysis, statistical software SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA) was used. P-values of 0.05 or less were considered statistically significant. All probability values were two-tailed.

Results

The characteristics of study subjects by MetS status and those without MetS are presented in table 1; 39 subjects (41.9%) had MetS. The two study groups were statistically similar in the average age, history of smoking, and serum level of low-density lipoprotein (LDL); while those with MetS were more female as well as had a higher prevalence of obesity, hypertension, hyperlipidemia, and diabetes mellitus. The mean level of plasma fibrinogen was not different in the two groups with and without MetS (240.10 ± 27.80 vs. 242.56 ± 35.82, P = 0.714), but the mean of cIMT was considerably higher in MetS group than in non-MetS group (0.85 ± 0.06 mm vs. 0.66 ± 0.09 mm, P < 0.001). Applying a linear regression modeling, among different definitive components of MetS, higher waist to hip ratio [β = 0.331, standard error (SE) = 0.138, P = 0.029], serum total cholesterol level (β = 0.002, SE = 0.001, P = 0.021), and high LDL cholesterol level (β = 0.002, SE = 0.001, P = 0.040) were positively associated with cIMT. However, none of the MetS components was associated with the level of plasma fibrinogen.

Considering 0.75 mm as the cut-off for high cIMT showed higher incidence of high cIMT in MetS group compared with non-MetS group (25.6% vs. 1.9%, P < 0.001). No significant association was revealed between plasma level of fibrinogen and cIMT in both MetS group (r = 0.018, P = 0.913) and non-MetS group (r = −0.052, P = 0.714). Using a multivariable logistic regression model (Table 2), it was shown that high cIMT could effectively predict MetS state with the presence of different components of MetS [odds ratio = 17.544, 95% confidence interval (CI) = 2.151-142.860, P = 0.008]. In this context, high level of plasma fibrinogen was not a determinant for MetS status. According to the ROC curve analysis (Figure 1), cIMT measurement had an acceptable value for discriminating MetS from non-MetS states [Area under curve (AUC) = 0.746, 95% CI = 0.644-0.848, P < 0.001]. The optimal cut-off point of cIMT for discriminating these two clinical states (Figure 2) was 0.6 mm yielding a sensitivity of 61.5% and a specificity of 59.6%.

Table 1. Baseline data in two groups with and without metabolic syndrome

Characteristics	Group with MetS (n = 39)	Group without MetS (n = 54)	P
Male gender	15 (38.5)	35 (67.3)	0.006
Hyperlipidemia	35 (89.7)	25 (48.1)	< 0.001
Diabetes mellitus	8 (20.5)	3 (5.8)	0.033
Hypertension	17 (43.6)	7 (13.5)	0.001
Cigarette smoking	7 (17.9)	18 (34.6)	0.078
High intima-media thickness	10 (25.6)	1 (1.9)	0.001
Body mass index (kg/m^2)	32.46 ± 5.52	26.71 ± 5.26	< 0.001
Waist to hip ratio	0.97 ± 0.06	0.89 ± 0.06	< 0.001
Fasting blood sugar (mg/dl)	100.87 ± 44.75	84.88 ± 14.35	0.018
Total cholesterol (mg/dl)	210.56 ± 41.79	193.33 ± 29.55	0.023
Serum triglyceride (mg/dl)	244.36 ± 134.56	119.06 ± 48.25	< 0.001
HDL (mg/dl)	41.41 ± 9.67	47.83 ± 11.77	0.005
LDL (mg/dl)	117.90 ± 24.87	111.67 ± 19.64	0.201
SBP (mmHg)	133.83 ± 19.38	119.62 ± 15.01	< 0.001
DBP (mmHg)	84.10 ± 10.06	76.63 ± 7.90	< 0.001
Plasma fibrinogen	240.10 ± 27.80	242.56 ± 35.82	0.083
Intima-media thickness (mm)	0.85 ± 0.06	0.66 ± 0.09	< 0.001
Age (year)	44.82 ± 6.09	47.31 ± 8.87	0.136

MetS: Metabolic syndrome; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SBP: Systolic blood pressure
DBP: Diastolic blood pressure

Table 2. Multivariate logistic regression model for determining value of high intima-media thickness and plasma fibrinogen to predict metabolic syndrome

Variables	P	Odds ratio	95% Confidence interval
High intima-media thickness	0.008	17.544	2.151-142.860
Plasma fibrinogen	0.395	0.991	0.970-1.012
Male gender	0.095	0.228	0.040-1.293
Age	0.139	0.906	0.796-1.032
Body mass index	0.028	1.210	1.021-1.435
Hyperlipidemia	< 0.001	35.546	4.889-258.443
Diabetes mellitus	0.670	1.603	0.184-13.991
Hypertension	0.007	15.848	2.093-119.993
Cigarette smoking	0.696	1.462	0.217-9.846

Hosmer–Lemeshow goodness of fit: χ^2 = 20.564; P = 0.008

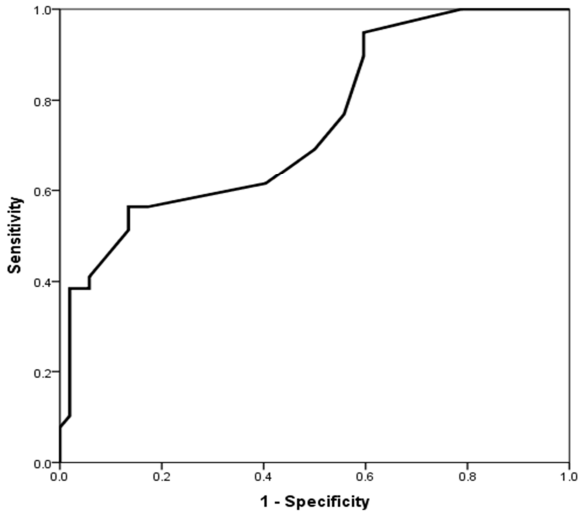

Figure 1. Receiver operating characteristic curves were constructed to investigate the diagnostic power of the intima-media thickness for predicting metabolic syndrome (area under curve = 0.746, 95% confidence interval = 0.644-0.848; P < 0.001)

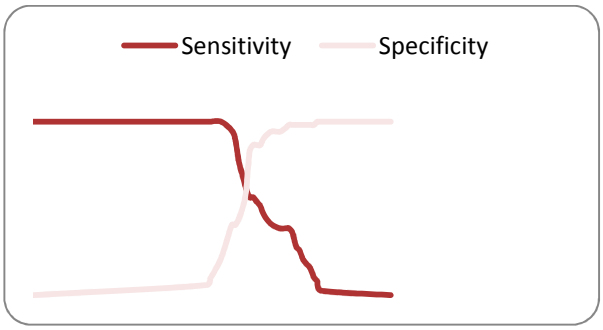

Figure 2. Optimal cutoff value of intima-media thickness for prediction of metabolic syndrome (best cutoff point was 0.6 mm)

Discussion

MetS significantly associated with increased cIMT in our cross-sectional study sourced from Isfahan prospective cohort analysis, and the association between MetS and incident high cIMT was considerably attenuated after controlling or different components of MetS in a multivariate logistic regression model. These findings suggest that the high cIMT can be an integral part of MetS. A variety of studies could show association between MetS and high cIMT. Reinehr et al. showed in subjects with MetS demonstrated increased intima-media thickness (IMT) values compared those without MetS.[4] In another study, MetS strongly predicted incident high cIMT, defined as cIMT > 90th percentile and/or plaque.[19] In this regard, it is now suggested that a combination of different components of MetS may have synergistic effects on existence and progression of carotid plaques resulting increased cIMT. Timoteo et al. could demonstrate that advanced age, male gender, insulin, and HDL cholesterol were independent predictors of cIMT. They showed that in patients without MetS, only age and HDL cholesterol were associated; while, in MetS group, independent predictors were age, male gender, and high serum glucose.[19] Tonstad et al. suggested that the classic lipid and hemostatic risk factors, as well as plasma total homocysteine, were associated with markers of early carotid atherosclerosis from the second decade of life.[20] According to the results of the Framingham study, the introduced Framingham risk factors accounted for 28.6% and 27.5% of the variability in the common carotid artery and internal carotid artery IMT, respectively. Furthermore, age and gender contributed 23.5% to the variability of the common carotid artery IMT and 22.5% to that of the internal carotid artery IMT, with the next most important factor being SBP (1.9%) for the common carotid artery IMT and smoking (1.6%) for the internal carotid artery IMT.[21] In another observation by Shiri et al., obesity, high LDL cholesterol, high triglycerides, hypertension and cardiac arrhythmia were associated with increased IMT in subjects aged 30-44.[22] Oren et al. also showed that

age, body mass index, pulse pressure, sex, and LDL cholesterol level were independent determinants of increased cIMT in young adults.[23] In our survey, higher waist to hip ratio, high serum total cholesterol level, and high LDL cholesterol level were positively associated with cIMT that is consistent with several previous studies.

Regarding the association between MetS state and plasma fibrinogen level, we found no significant association between these two parameters. On the other hand, although relation between inflammatory processes and MetS has been shown in some studies, but association between fibrinogen as an inflammatory index and MetS and its-related components was not meaningful in our study. Imperatore et al. showed that age-adjusted fibrinogen levels correlated significantly with obesity, SBP and DBP, plasma total cholesterol, LDL cholesterol, triglycerides, insulin, and HDL cholesterol inversely.[11] In a study by Ford,[24] participants with the MetS had higher fibrinogen concentrations than those without this syndrome. Besides, the association between fibrinogen level and MetS was only demonstrated in women, not in men in Onat et al. study.[12] On the other hand, MetS was not significantly predicted by fibrinogen levels in women in either multivariable model and thus plasma fibrinogen predicts MetS independently of its components in men, in contradistinction to women. It seems that our paradoxical findings may be affected by different factors such as selecting a population with a narrow range for plasma fibrinogen concentration, a wide range of the patients' age, as well as considering a partial small sample size and therefore achieving a moderate study power. Hence, for more investigation of the association of plasma fibrinogen concentration and MetS state, further studies should be conducted in our population.

Our results are limited to our small size but in this is the first report in Iranian sample, which focused on the relationship of cIMT and fibrinogen and would be provide a view of the procedure in this population.

Conclusion

Our study demonstrate that measuring cIMT can help to predict MetS state, however measuring plasma fibrinogen has no this potential predictive role. In fact, association between MetS and cIMT can be mediated by the presence of some MetS components including waist to hip ratio, high serum total cholesterol level, and high LDL cholesterol level.

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Conflict of Interests

Authors have no conflict of interests.

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