Coronary Heart Disease

Rheumatoid Factor is a Strong Risk Factor for Coronary Artery Disease in Men with Metabolic Syndrome

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Background: Recent studies have indicated an association between the autoantibody rheumatoid factor (RF), a circulating marker of inflammation, and coronary artery disease (CAD). However, the relation between the level of circulating RF and CAD in patients with metabolic syndrome (MS) has not been well documented.

Methods: We prospectively studied a total of 219 consecutive patients who underwent coronary angiography during the period February 2007 to December 2009. These patients were divided into three groups. The control group comprised 38 patients with no significant CAD (coronary artery stenosis < 50%, all segments of three vessels). The MS group consisted of 57 patients with no significant CAD. The MS/CAD group comprised 124 patients with significant CAD. Plasma RF was measured before coronary angiography.

Results: The mean RF levels were 5.21 IU/mL in the control group, 6.75 IU/mL in the MS group, and 9.28 IU/mL in the MS/CAD group. In the MS and MS/CAD groups, multiple logistic regression analysis using binary analysis for males and females variables showed that elevated plasma RF level ($\geq$ 6.0 IU/mL) was a significant predictor of significant CAD (OR = 3.13, 95% CI 1.12-8.77, p < 0.05) in men. The RF level was not associated with the presence of significant CAD in women.

Conclusion: Elevated plasma RF is an independent risk factor for CAD in men with MS. This finding implies an important relationship between inflammation and atherosclerosis and suggests that autoimmune processes may be involved in the development of CAD in men with MS.

Key Words: Coronary artery disease ● Man ● Metabolic syndrome ● Rheumatoid factor

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death worldwide.[1] Most patients with CAD have one or more traditional risk factors, including diabetes, a history of smoking, hypertension, obesity, and a family history of CAD or hyperlipidaemia.[2,3] In recent years, new risk factors for CAD have been identified, including the presence of inflammation as demonstrated by raised levels of high-sensitivity C reactive protein (hs-CRP).[4-6] Subjects with chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus also have a greatly increased risk of developing CAD.[7,8]

Rheumatoid factor (RF) is strongly associated with

RA and may be present in subjects many years before they develop RA, and its presence confers a risk of developing RA that increases with increasing titre.[8,9] However, RF is associated with other autoimmune rheumatic diseases, as well as with viral or bacterial infections, and is present in as many as 15% of normal adults. Recently, RF has been shown to be associated with an increased likelihood of developing CAD in patients with rheumatoid arthritis.[8]

Metabolic syndrome (MS) is characterized by a group of metabolic risk factors, including obesity, dyslipidemia, hypertension, insulin resistance, and a prothrombotic and proinflammatory state.[10,11] Patients with MS are at increased risk for cardiovascular morbidity and mortality.[10-13] Early recognition and appropriate non-pharmaceutical approaches including lifestyle changes, diet, and exercise may decrease long-term morbidity and mortality.[13] We hypothesized that the presence of RF in a MS population may identify those at increased risk of developing CAD, and that RF may play a special role in the pathogenesis of CAD. To explore this, we investigated whether RF is a risk factor of CAD in patients with MS.

MATERIALS AND METHODS

Patients

In this prospective study, we enrolled 219 consecutive patients who underwent coronary angiography during the period February 2007 to December 2009. The purpose of the study was explained to each patient, and all signed consent forms. Medical histories including smoking habit, diabetes mellitus, dyslipidemia, and current medications were taken. For the purpose of this study, the serum levels of hs-CRP, RF, and routine tests such as fasting plasma glucose (FPG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol of all patients who underwent coronary angiography were prospectively measured. Blood samples were drawn after vascular puncture before coronary angiography was performed in the cardiac catheterization room. Enzyme-linked immunosorbent assay was used to measure RF. The patients were divided into two groups according to the baseline RF level: an RF < 6 IU/mL group and an RF ≥ 6 IU/mL group. Patients with

malignancies, acute or chronic renal failure (creatinine > 1.5 mg/dL), chronic liver diseases, hyper- or hypothyroidism, febrile disorders, acute or chronic inflammatory disease at study entry, history of recent infection, or heart failure were excluded. The eligible patients were allocated into a control group consisting of 38 patients with no significant CAD (coronary artery stenosis < 50%, all segments of three vessels), an MS group comprising 57 patients with no significant CAD, and an MS/CAD group consisting of 124 patients with significant CAD. The institutional review board of the Armed Forces Taichung General Hospital approved this study.

Definition of metabolic syndrome

The definition of MS was based on the ATP III recommendations with some modification. The clinical components of MS include abdominal obesity, high triglycerides, low high-density lipoprotein-cholesterol, high blood pressure, and high fasting glucose. According to the Adult Treatment Panel (ATP) III criteria, the diagnosis of MS is made when 3 or more of the following risk determinants are present: abdominal obesity (waist circumference: men > 102 cm; women > 88 cm), high TG (≥ 150 mg/dL), low HDL-C (men < 40 mg/dL; women < 50 mg/dL), high blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg), and high FPG (≥ 110 mg/dL).[14] Since the ATP III criteria for abdominal obesity might not be appropriate for Chinese, the cut-offs for waist circumference used in this study were > 90 cm in men and > 80 cm in women.[15]

Statistical analysis

Continuous variables are presented as means ± SD. Comparisons were conducted by Student's t-test. Discrete variables are presented as percentages and relative frequencies, and comparisons were conducted using the chi-square test or Fisher's exact test as appropriate. To determine the independent predictors of CAD in patients with MS, we performed multivariate logistic regression analysis using binary analysis for male and female variables and linear regression for continuous variables. Statistical analyses were performed using SAS statistical software for Windows version 8.2 (SAS Institute, Cary, NC). A p value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

The numbers of men and hypertension were significantly higher in the MS/CAD group than in the MS group. There were no significant differences in age, current smoking status, diabetes mellitus, dyslipidemia, previous myocardial, family history of infarction, body mass index, hs-CRP, creatinine at admission, RF, or left ventricular ejection fraction between the two groups (Table 1).

Variation of circulating levels of inflammatory markers between study patients and control group subjects

There was no significant difference in mean level of hs-CRP between the control group (1.25 ± 0.85 mg/L), the MS group (1.75 ± 0.68 mg/L), and the MS/CAD group (1.89 ± 0.85 mg/L) (p > 0.05) (Table 1). The mean RF level in the MS/CAD group was significantly higher than that in the MS group and control group (9.28 ± 1.80 IU/mL vs. 6.75 ± 1.28 IU/mL, or 9.28 ± 1.80 IU/mL vs. 5.21 ± 1.78 IU/mL; p < 0.05) (Table 1). The circulating level of RF did not significantly differ between patients with MS without CAD and patients in the control group (6.75 ± 1.28 IU/mL vs. 5.21 ± 1.78 IU/mL; p = 0.38).

Multiple logistic regression analysis

Multiple logistic regression analysis of traditional CAD risk factors using binary analysis for male and female variables and clinical variables at enrollment demonstrated that RF and male gender were significantly and independently associated with CAD [odds ratio (OR) = 3.13, 95% confidence interval (CI): 1.12-8.77, p < 0.05] (Table 2).

Table 2. Independent predictive factors for coronary artery disease in patients with metabolic syndrome

Drugs	OR	95% CI	P value
Age	1.03	1.00-1.06	0.051
Current smoking	2.08	0.84-5.14	0.112
Hypertension	2.12	0.80-5.63	0.131
Diabetes mellitus	3.15	1.30-7.66	0.011
Dyslipidemia	1.39	0.64-3.02	0.411
Hs-CRP	0.72	0.30-1.92	0.753
Male RF	3.13	1.12-8.77	0.030
Female RF	0.54	0.21-1.36	0.411

RF, rheumatoid factor.

Table 1. Baseline characteristics of all patients

Variables	MS (+) CAD (−) (N = 57)	MS (+) CAD (+) (N = 124)	MS (−) CAD (−) (N = 38)	MS (−) CAD (+) (N = 38)
Age (years) (mean ± SD)	65 ± 13	67 ± 14	64 ± 12	68 ± 12
Male gender (%)	28 (49)	80 (65)*	15 (49)	26 (68)
Current smoking (%)	14 (38)	53 (43)	10 (26)	24 (63)
Hypertension (%)	32 (68)	108 (87)*	27 (70)	33 (87)
Diabetes mellitus (%)	17 (30)	46 (37)	3 (8)	10 (26)
Dyslipidemia (%)	24 (42)	60 (48)	10 (26)	12 (32)
Familiar history of AMI	9 (16)	22 (18)	1 (3)	3 (8)
Previous MI	2 (5)	3 (5)	0 (0)	2 (5)
Creatinine at admission	1.12 ± 0.28	1.10 ± 0.25	1.08 ± 0.32	1.10 ± 0.30
Body mass index (kg/m^2)#	28.4 ± 4.8	29.1 ± 4.4	22.8 ± 5.6	22.4 ± 5.8
LVEF during hospitalization	64 ± 10	65 ± 11	68 ± 16	67 ± 17
Hs-CRP (mg/dl)	1.75 ± 0.68	1.89 ± 0.85	1.25 ± 0.85	1.20 ± 0.96
RF (IU/mL)	6.75 ± 1.28	9.28 ± 1.80*	5.21 ± 1.78	5.36 ± 1.70

Data are expressed as mean ± SD. AMI, acute myocardial infarction; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; RF, rheumatoid factor.

#Body mass index was defined as the weight in kilograms divided by the square of the height in meters (kg/m^2).

*Represents statistical significance between metabolic syndrome (MS) without coronary artery disease (CAD) and MS with CAD patients (p value < 0.05).

DISCUSSION

Our results appear to show an association between RF and an increased risk of CAD in men with MS. This was independent of traditional risk factors, and the magnitude of association was similar to that for type 2 diabetes in this study.

RF is present in up to 15% of elderly subjects and may arise through polyclonal B cell activation due to infectious organisms or by antigen-driven proliferation of B cells associated with autoimmune diseases, including RA.[7,8] Although RF is strongly associated with RA and RA is associated with increased cardiovascular morbidity and mortality, the increased risk in our study is unlikely to be due to active RA or its treatment.[8,9] Some studies have reported that higher level of RF is an independent risk factor for CAD in men from the general population.[8,9] Our result is the same as that reported by Edwards et al.[8] They investigated whether the presence of RF was associated with an increased risk of CAD among a population of elderly men and women in the Hertfordshire Cohort Study (HCS). They found that RF was associated with an increased likelihood of CAD in men (OR = 3.1, 95% CI 1.7 to 5.4, p < 0.001) but not in women.

Arterial inflammation can progress to atherosclerosis, the primary pathologic process in CAD and other cardiovascular diseases.[6] Several studies have demonstrated that higher levels of hs-CRP are associated with an increased risk of long-term cardiovascular morbidity and mortality in patients with MS.[12,17-19] Clinically, CRP is related to adverse outcomes in patients with acute coronary syndromes.[20] In our study, we found that hs-CRP was not an independent risk factor for CAD in patients with MS, a finding that contradicts those in previous reports. Our result might be due to the fact that all three groups of patients had relatively stable angina pectoris.

MS has been recognized recently as a predictor of CAD.[11,12] MS with CAD appears to increase the risk for long term cardiovascular morbidity and mortality.[10-13] Recent studies have indicated that patients with MS have significantly higher levels of inflammatory markers than healthy individuals.[10,18] As a result, early detection of patients with MS at high risk for CAD and implementation of appropriate nonpharmaceutical approaches including lifestyle changes, diet, and exercise may decrease the long-term morbidity and mortality rate in patients with MS. Our results indicate that RF is a better indicator of CAD than hs-CRP, suggesting that RF could be an additional inflammatory marker for risk stratification in patients with MS.

Two limitations in this study need to be emphasized. First, this was a cross-sectional study and will therefore need confirmation in a longitudinal cohort study. So caution must be exercised in interpreting our data. Secondary, this was a prospective study at local hospital in Taiwan over a period of two years. We performed analyses restricted to participants who signed consent form during the study; therefore, it is not clear how our findings can be generalized to patients in different areas.

CONCLUSION

In conclusion, we found that men with MS and CAD had significantly higher plasma RF levels than male MS patients without CAD. Based on this finding, we suggest that increased RF levels can serve as a marker to help identify men with MS who are at risk of developing CAD. This finding also provides some explanation of the pathogenesis from MS to CAD.

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