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Concise Report

Metabolic syndrome is associated with disease activity in patients with rheumatoid arthritis

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ABSTRACT

Objective: To investigate the association between metabolic syndrome (MS) and disease activity in patients with rheumatoid arthritis (RA).
Methods: Siriraj Rheumatoid Arthritis registry is a prospective cohort study establishing since May 2011. A total of 267 patients who had complete data in February 2015 were included in these analyses. All clinical and laboratory data related to disease activity, functional status, and parameters of MS according to the 2001 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) were collected. Univariate and backward stepwise multivariate analyses were performed to identify factors associated with MS.
Results: Most (88%) were female with the mean age ± standard deviation of 59 ± 11.1 years old. MS was found in 43 patients (16%). Patients with MS had a significantly lower proportion of patients with remission (time-adjusted mean of disease activity score 28 or DAS28 < 2.6) than those with non-MS (2.3% vs. 16.5%, $P = 0.02$). Multiple logistic regression analysis identified 3 independent factors associated with MS including body mass index [OR 1.2, 95% CI 1.1 to 1.3], educational level ≤ 12 years [OR 5.92, 95% CI 1.47 to 23.83], and disease remission [OR 0.11, 95% CI 0.01 to 0.93]. This model correctly predicted 84% of cases.
Conclusion: Remission rate is significantly lower in RA patients with MS. Disease activity of RA, body mass index, and educational level are associated with metabolic syndrome in patients with RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease involving articular and extra-articular systems, including cardiovascular (CVS), respiratory, as well as hematologic systems, etc. Among extra-articular manifestations, CVS disease is a leading cause of morbidity and mortality in the recent years. A systematic review and meta-analysis of cohort studies showed that RA is associated with 60% increase in CVS death compared with general population [1]. Incidence of CVS events in patients with RA is higher than what would be expected in individuals without RA. This could not be explained by traditional CVS risk factors alone. Solomon et al. found that patients with two or more traditional CVS risk factors and three or more makers for RA disease severity had a higher risk for CVS events than those with or without either factors [2]. Consequently, optimal control of only traditional CVS risk factors is important, it is insufficient to reduce CVS risk for these patients. It has been shown in previous study that disease severity and activity are associated with CVS mortality [2]. Additionally, treatment with methotrexate (MTX), a disease-modifying anti-rheumatic drugs (DMARDs), has been shown to decrease CVS risk and is thought to be due to effective, long-term, suppression of systemic inflammation [3].

Metabolic syndrome (MS) is associated with approximately 2-fold increased risk of CVS diseases [4]. Patients with RA also have increased risk of MS, compared to general population [5,6]. However, this risk was various among different ethnicities and definition used [5–8]. Prevalence of MS in patients with RA was higher in Mediterranean area than in Asia, 44% in Greece [5], 32.3% in Morocco [6] compared with 19% in South Korea [8] and 16–41% in Vietnam [9]. The high prevalence of MS in RA may be attributed to chronic systemic inflammatory state [10], immobilization [11], and medications for RA treatment [12,13]. Conversely, there is evidence supporting that the use of MTX to suppress inflammation significantly reduced the prevalence of MS in patients with RA [14].

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Chronic systemic inflammation from both RA and MS could promote endothelial dysfunction and atherosclerotic plaques development leading to increase in CVS risk [11]. To reduce CVS morbidity and mortality in RA, suppression of inflammation should be achieved to decrease the occurrence of MS.

This study aimed to elucidate prevalence and factors associated with MS in patients with RA including RA disease activity. The results would lead physicians to identify high-risk patients and apply strategies to prevent CVS disease in the future.

2. Methods

2.1. Study population

Siriraj Rheumatoid Arthritis (SIRA) registry is a prospective cohort establishing since May 2011 from outpatient service of Division of Rheumatology, Department of Medicine, Faculty of Medicine, Siriraj hospital, Bangkok, Thailand. All patients (350) in SIRA registry were invited to enroll in this study; however, only 267 patients who had complete data in February 2015 were included in these analyses. All patients were diagnosed of RA according to the 2010 American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) classification criteria [15]. They were excluded if they were diagnosed of overlap syndrome with other rheumatic or autoimmune diseases. Informed consents were obtained from all patients. The study was approved by the Siriraj Institutional Review Board (SIRB) and has been conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the principles outlined in the Guideline for Good Clinical Practice International Conference on Harmonization Tripartite Guideline (January 1997).

2.2. Clinical and laboratory assessments

Demographic, clinical, and laboratory data related to disease activity, functional status, and medications were collected at baseline and every 3 months. Data related to disease activity included the duration of morning stiffness, pain score on a 0–10 centimeters (cm) of visual analogue scale (VAS), patient's global assessment of disease activity (0–10 cm VAS), physician's global assessment of disease activity (0–10 cm VAS), the number of tender joint (TJC) (68 joints), the number of swollen joint (SJC) (66 joints), erythrocyte sedimentation rate (ESR). Disease Activity Score 28 (DAS28) was calculated [16]. Functional status was assessed using the Thai version of Health Assessment Questionnaire (HAQ) [17].

Parameters of MS according to the 2001 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [18] of each patient were collected once during July 2013 and February 2015. Waist circumference (WC) was measured by placing a measuring tape in a horizontal plane around abdomen at level of iliac crest in the end of a normal expiration [19,20]. WC for abdominal obesity is defined as WC $\geq$ 102 cm for men and $\geq$ 88 cm for women [18]. Body mass index (BMI) was calculated from weight in kilograms divided by height in meters squared (kg/m^2). BMI cut-off points are based on WHO recommendations for Asian populations. BMI of less than 18.5 kg/m^2 is considered as underweight, 18.5–23 kg/m^2 as normal, 23–27.5 kg/m^2 as overweight, and 27.5 kg/m^2 or higher as obese [21]. Blood pressure was measured by a mercury sphygmomanometer in the sitting position after five minutes of rest.

Venous blood samples were collected for biochemical tests. Rheumatoid factor (RF) was analyzed by immunoturbidimetry assay in 2011–2013 and enzyme linked immunosorbent assay (ELISA) in 2013–2015, anti-cyclic citrullinated peptide (anti-CCP) by ELISA in 2011–2014 and chemiluminescent microparticle immunosorbent assay (CMIA) in 2014–2015, erythrocyte sedimentation rate (ESR) by automated method using Vesmatic Easy machine, fasting blood glucose by enzymatic (hexokinase) method, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) were measured by enzymatic colorimetric assay.

2.3. Metabolic syndrome

Criteria for clinical diagnosis of MS are adopted according to 2001 NCEP ATP III, as it is the most and widely used definition reported in the literature, thus allowing for comparison between studies. MS is defined as the presence of three or more of the following 5 components: abdominal obesity: waist circumference > 102 cm in men and > 88 cm in women, elevation of serum triglycerides: > 150 mg/dL or specific treatment for this lipid abnormality, low HDL-C: < 40 mg/dL in men and < 50 mg/dL in women or specific treatment for this lipid abnormality, high blood pressure: $\geq$ 130/85 mmHg or treatment of previously diagnosed hypertension, and high fasting glucose: $\geq$ 110 mg/dL or treatment of previously diagnosed type 2 diabetic mellitus [18].

2.4. Cumulative disease activity

For cumulative disease activity, time-adjusted mean (TAM) of DAS28 was calculated. The TAM of DAS28 is the area under a curve (AUC) of DAS28 plotted against time, divided by the total length of time from first to last measurement. It is more accurate for estimating cumulative disease activity because it takes into consideration the time interval between DAS28 measurements, especially when the time interval between DAS28 measurements might be irregular.

2.5. Statistical analysis

Statistical analysis was performed with PASW 18 SPSS (SPSS Inc., Chicago, IL, USA). Student *t*-test or Mann-Whitney U test was used to compare continuous quantitative data and Chi^2 test for qualitative data. Univariate analysis was performed to identify potential factors related to the presence of MS. Factors that were identified to be different between patients who had or did not have MS with *P*-value < 0.2 in univariate analysis or factors that have been reported in previous studies to be associated with MS in RA were then included in multivariate analysis. Backward stepwise logistic regression analysis was performed to identify independent factors associated with MS in RA patients. Statistical significance was defined as the *P*-value < 0.05, two-sided.

3. Results

Among 267 RA patients, most (88%) were female with the mean age $\pm$ standard deviation (SD) of 59 $\pm$ 11.1 years old, and median disease duration (interquartile range or IQR) of 11.5 (6.5–17.7) years. The median duration of follow-up (IQR) was 36 (30–39) months. RF and anti-CCP were presence in 70.4% and 72.4%, respectively. Mean cumulative disease activity (mean TAM of DAS28) was 3.42. Thirty-eight (38) patients (14.2%) had TAM of DAS28 of lower than 2.6.

MS was found in 43 patients (16%) and 90.7% were female. No significant differences were observed in sex, disease duration, presence of RF and anti-CCP, alcohol and smoking status, dose of RA medications, and medication use, except rituximab.