# Rheumatoid arthritis may be one step further of systemic lupus erythematosus

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## Abstract

Background: We tried to understand whether or not there are some relationships between rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) according to mean age of onset, frequency, and gender distribution in society.

Methods: The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients applying to the Internal Medicine Policlinic were included in the study.

Results: The study included 223 males and 210 females, totally. Their mean ages were 30.4 versus 30.3 years, respectively ($p>0.05$). SLE was diagnosed in 6.0% of them (24 females and two males), and 92.3% of the SLE patients were female. Mean age of the SLE cases was 37.0 ± 13.6 (17-58) years. On the other hand, RA was diagnosed in 2.7% of them, so SLE was much more frequent in society ($p<0.001$). Beside that 50.0% of the RA patients were female (six females and six males), so female predominance of the SLE was higher than RA ($p<0.001$). Mean age of the RA patients was 44.5 ± 7.6 (30-57) years, so RA patients were significantly older than the SLE patients ($p= 0.038$).

Conclusion: Because of the similar clinical presentation types, similar treatment agents, similar prognosis, and difficulties in differential diagnosis, RA may be one step further of the SLE due to its lower prevalence in society (2.7% versus 6.0%, $p<0.001$), similar prevalence in both genders (50.0% versus 92.3% in females, $p<0.001$), and higher mean age of onset (44.5 versus 37.0 years, $p= 0.038$).

Key words: Rheumatoid arthritis,
systemic lupus erythematosus, chronic endothelial damage, atherosclerosis, metabolic syndrome

## Introduction

Chronic endothelial damage may be the major cause of aging and associated morbidity and mortalities by causing tissue hypoxia and infarctions all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are mainly involved in the process. Some of the well-known accelerator factors of the inflammatory process are physical inactivity, excess weight, smoking, alcohol, chronic inflammation and infections, and cancers for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). The syndrome is characterized by a chronic low-grade inflammatory process on vascular endothelium all over the body (3, 4). The syndrome has become so common all over the world, for example 50 million people in the United States were affected (5). Physical inactivity induced excess weight may be one of the major underlying causes of the syndrome. Excess weight is a disorder characterized by increased mass of adipose tissue. The chronic inflammation induced endothelial dysfunction may be the action of excess weight for the increased atherogenicity (6-9). Probably chronic vascular endothelial inflammation including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) may also accelerate the premature aging process, and terminate with end-organ insufficiency and premature death. We tried to understand whether or not there are some relationships between RA and SLE according to the mean age of onset, frequency, and gender distribution in society.

## Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients applying to the Internal Medicine Polyclinic were included into the study. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. Cases with another inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, hepatic function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest X-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, and an abdominal ultrasonography was performed. Patients with RA were classified with the criteria of early rheumatoid arthritis (ERA) (10). The ERA criteria include a morning stiffness of 30 minutes or longer, arthritis of three or more joint areas, arthritis of hand joints, positivity of rheumatoid factor (RF), and positivity of anti-cyclic citrullinated peptide antibody (anti-CCP). RA is defined by the presence of three or more of the criteria. SLE is classified with the criteria of the American College of Rheumatology of 1997 including discoid rash, immunologic features, photosensitivity, neurologic disorders (headache, depression, seizures, and psychosis), oral ulcers, malar rash, arthritis, serositis, hematologic disorders (leukopenia, lymphopenia, thrombocytopenia, and hemolytic anemia), antinuclear antibodies (ANA), and renal involvement (proteinuria, low complement, red blood cell casts, granular casts) (11). Four of them are required for classification but not for diagnosis. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (12). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (13). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination, liver function tests, ultrasonographic evaluation, and tissue samples in case of indication. An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CAD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Eventually prevalence, mean ages of onset, and gender distributions of RA and SLE were detected in society and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 223 males and 210 females, totally. Their mean ages were 30.4 versus 30.3 years, respectively ($p>0.05$). SLE was diagnosed in 6.0% and 92.3% of the SLE patients were female (24 females and two males). The mean age of SLE cases was 37.0 ± 13.6 (17-58) years. On the other hand, RA was diagnosed in 2.7%, so SLE was much more frequent in the society ($p<0.001$). Beside that 50.0% of the RA patients were female (six females and six males), so female predominance of the SLE was higher than RA ($p<0.001$). The mean age of RA patients was 44.5 ± 7.6 (30-57) years, so the RA patients were significantly older than the SLE patients ($p= 0.038$) (Table 1).

**Table 1: Characteristic features of the study patients**

| Variables | Patients with SLE* | *p*-value | Patients with RA† |
|---|---|---|---|
| Prevalence | 6.0% (26) | <0.001 | 2.7% (12) |
| Mean age (year) | 37.0 ± 13.6 (17-58) | 0.038 | 44.5 ± 7.6 (30-57) |
| Female ratio | 92.3% (24) | <0.001 | 50.0% (6) |

*Systemic lupus erythematosus †Rheumatoid arthritis

## Discussion

Chronic endothelial damage may be the leading cause of early aging and premature death in human beings. Physical inactivity, excess weight, smoking, alcohol, chronic inflammation and infections, and cancers may accelerate the process (14-16). Probably, it is the most common type of vasculitis all over the world. Whole afferent vasculature including capillaries may mainly be involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Thus the term venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the continuous endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Although early withdrawal of the causative factors may retard the final consequences, after development of HT, DM, cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic natures (17).

RA is a common and chronic syndrome, characterized by non-specific but usually symmetric inflammation and synovial hypertrophy of the peripheral joints, potentially terminating with progressive destruction of articular and periarticular tissues with or without systemic manifestations (18). It typically affects small joints of the hands and feet, but it can also affect larger joints (19). Fever, subcutaneous and visceral nodules, pleural and pericardial effusions, lymphadenopathy, splenomegaly, cytopenias, and episcleritis are just some of the samples of the extra-articular manifestations. Diagnosis is based on duration of symptoms, joint distribution, acute phase reactants, and autoantibodies including RF and anti-CCP (20). The presence of clinical or subclinical synovitis seen with ultrasonography or magnetic resonance imaging is essential for diagnosis. RA can sometimes present with a large joint monoarthritis or oligoarthritis. In cases presenting with monoarthritis, careful assessment for differential diagnosis is needed, particularly in the elderly patients where other conditions such as gout, calcium pyrophosphate deposition disease, and osteoarthritis are common (21). Early referral of patients with suspected synovitis, particularly in small joints of hands and feet, is important in long-term outcomes (22). On the other hand, RA may mimic several systemic disorders, particularly in young and middle-aged females due to the extra-articular manifestations. According to our experiences, the diagnosis of RA requires highly trained specialists who are able to differentiate early symptoms of RA from other pathologies, particularly from SLE. SLE can be distinguished by the characteristic skin lesions on light-exposed areas, oral aphthous lesions, nonerosive arthritis, positive antibodies to double-stranded DNA, renal and central nervous system (CNS) involvements, and thrombocytopenia. Although RA and SLE have similar agents in the treatment protocol, ANA and anti-double-stranded DNA antibodies should be studied in every patient suspected from RA.

SLE is an autoimmune disease characterized by skin lesions on sun-exposed areas, oral lesions, nonerosive arthritis, fever, positive antibodies to double-stranded DNA, renal and CNS involvements, and cytopenias (23). It is mostly seen in women with a younger mean age (23). Similarly, 92.3% of all SLE patients were female, and mean age of the SLE cases was 37.0 years in the present study. Additionally, the prevalence of SLE was significantly higher than RA in the society, here (6.0% versus 2.7%, p<0.001). The higher prevalence of marriage with close relatives may be an underlying cause of such high prevalences of RA and SLE in Turkey. The sera of most patients contain ANA, often including anti-double-stranded DNA antibodies (24). Articular symptoms are seen in 90% of patients, and they may exist for many years before the diagnosis (25). For instance, the average time from the onset of symptoms to diagnosis was five years in the above study (23). As a difference from RA, the majority of the polyarthritis of SLE is nondestructive in nature. Cutaneous lesions include characteristic malar butterfly erythema, discoid lesions, and erythematous, firm, and maculopapular lesions on sun-exposed areas of face, neck, upper chest, and elbows. Photosensitivity is seen in 40% of cases. Generalized lymphadenopathy is also common. CNS involvement may cause personality changes, stroke, epilepsy, and psychoses (26). Renal involvement may be silent or even fatal. The most common manifestation is proteinuria (27). There were increases in the prevalence of renal involvement and neurological symptoms throughout the disease course (23). Differential diagnosis of SLE from other pathologies may be difficult. For example, early-stage SLE can be difficult to differentiate from RA if arthritic symptoms predominate (18-20). On the other hand, clinicians in the Hematology Clinics should be aware of SLE due to the frequent thrombocytopenia in differential diagnosis, particularly with idiopathic thrombocytopenic purpura. Immunosuppressive therapy has made it possible to control the disease with improved life expectancy and quality of life (27). According to our observations, methotrexate may be the simplest, cheapest, orally used, and one of the most

effective treatment regimens for both SLE and RA. It can suppress inflammation and reduce corticosteroid dosage. But although the majority of the patients' inflammation can be controlled effectively with methotrexate alone, most of the patients need additional low dose corticosteroid for obstinate pain during the therapy with unknown reasons yet. Benefit of methotrexate initiates after a period of 3 to 4 weeks. It can be given 2.5 to 20 mg in a single dose once weekly, starting with a dosage of 7.5 mg per week.

As a conclusion, because of the similar clinical presentation types, similar treatment agents, similar prognosis, and difficulties in differential diagnosis, RA may be one step further of the SLE due to its lower prevalence in the society (2.7% versus 6.0%, $p<0.001$), similar prevalences in both genders (50.0% versus 92.3% in females, $p<0.001$), and higher mean age of onset (44.5 versus 37.0 years, $p=0.038$).

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