

CLINICAL LITERATURE REVIEWS

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Cardiovascular disease is a major cause of morbidity and mortality in adults, and myocardial infarction is more common in SLE patients than in the general population. As the risk of cardiovascular disease increases with disease duration, early diagnosis and aggressive treatment of children with SLE may be crucial in preventing and/or minimizing risk of atherosclerotic heart disease. The following two adult studies raise important questions of whether there may be early lesions in the coronary arteries in the pediatric age group and what might be the best method of stratifying risk, preventing, detecting, monitoring and managing symptomatic and asymptomatic atherosclerotic cardiovascular disease in children with SLE.

1. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *New England Journal of Medicine.* 349(25):2399-406, 2003 December 18.

Authors: Roman MJ. Shanker BA. Davis A. Lockshin MD. Sammaritano L. Simantov R. Crow MK. Schwartz JE. Paget SA. Devereux RB. Salmon JE.
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REVIEW

This article substantiates the hypothesis that systemic lupus erythematosus (SLE) has atherogenic potential because of chronic immune activation that is independent of traditional risk factors. This novel case-controlled study

examines the prevalence of atherosclerosis and risk factors in SLE patients, and determines if disease-related factors, treatment, and immune and inflammatory mediators are separately related to the development of atherosclerosis in SLE.

Salmon et al enrolled 197 SLE patients greater than 18 years of age over a 30-month period. Each patient fulfilled the ACR criteria and was matched to a control based on age, sex, race and blood pressure. Each variable has been strictly operationalized as evidenced by the following brief account of the methodology.

The presence of atherosclerotic plaque was determined by ultrasonography of extracranial carotid arteries, and was defined as a “focal protrusion of more than 50 percent of the surrounding wall.” Echocardiography on all subjects included determination for the presence of pulmonary hypertension, Libman-Sacks lesions, pericardial thickening and effusion. The following traditional risk factors were examined: presence or absence of family history of premature myocardial infarction (prior to 55 years in first degree male relatives or before 65 years in female relatives); hypertension; (blood pressure of at least 140/90 mm Hg or the use of antihypertensive medication); diabetes mellitus; smoking status; fasting cholesterol level.

SLE Disease Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SLICC), and medication use, including corticosteroid therapy (current, former or none), were assessed. Average daily corticosteroid dose over 5 years was calculated. The following laboratory analyses were performed: complete blood count, complements, anti-ds-DNA, Sm, RNP and antiphospholipid antibody, C-reactive protein, CD40 ligand, and Lp (a) lipoprotein by cholesterol content, IL-6, TNF p55 and p75 receptors, soluble intracellular adhesion molecule 1 and vascular cell adhesion molecule 1.

Mann-Whitney U and chi-square tests were performed for comparison of groups. Stepwise, forward-selection logistic-regression was used to determine the independence of the association with atherosclerosis. As elucidated above, the study design and variables chosen render adequate depth to the analysis.

Salmon et al found that the patients and controls were comparable in terms of demographic and risk factors for cardiovascular disease, except that the controls had a higher blood pressure as compared to patients at the time of the study. Atherosclerosis (plaque) was more prevalent in SLE patients than the controls in all age groups (37.1 percent vs. 15.2 percent, $P < 0.001$). In patients less than 40 years of age, the prevalence was 5.6 times higher than in matched controls. Multivariate analysis revealed that older age, the presence of SLE (odds ratio, 4.8; 95 percent confidence interval, 2.6 to 8.7), and a higher serum cholesterol level were the only factors that were separately associated with the presence of atherosclerosis. Repeating analysis after excluding patients with clinical cardiovascular disease did not affect the results.

The authors found that as compared to patients without plaque, SLE patients with plaque were older, had a greater disease duration, higher disease-related damage score and more disease-related damage (as opposed to medication-related damage). They were less likely to have multiple autoantibodies (Ro, La, Sm, RNP, anticardiolipin antibodies) or to have received prednisone, cyclophosphamide, or hydroxychloroquine. Inflammatory mediators were increased in SLE patients as compared to controls, but a statistically significant difference was not found between patients with and without atherosclerosis.

Finally, in multivariate analyses, Salmon et al found several independent predictors of atherosclerosis: older age of diagnosis, longer disease duration, higher damage score, a lower use of cyclophosphamide, and the absence of anti-Smith or anticardiolipin antibodies. Limiting the analysis to SLE patients who developed the disease when they were younger than 35 years of age, the authors substantiated the relationship of atherosclerosis with increased disease duration, high damage score, and lack of immunosuppressive medication. These results led the authors to conclude that SLE is an independent risk factor for atherosclerosis.

This study implicates disease-related factors, including chronic inflammation, as playing a significant role in atherogenesis and emphasizes the

importance of future studies characterizing the role of inflammatory markers, autoantibodies, and effect of medications. The significant association of increased disease duration and cumulative damage with premature atherosclerosis strongly suggests that early and aggressive intervention by pediatric rheumatologists may be crucial in preventing premature coronary artery disease in young adults with SLE.

2. Premature coronary-artery atherosclerosis in systemic lupus

erythematosus. New England Journal of Medicine. 349(25):2407-15, 2003 December 18.

Authors: Asanuma Y. Oeser A. Shintani AK. Turner E. Olsen N. Fazio S. Linton MF. Raggi P. Stein CM.

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REVIEW

In this case-control study, Stein et al has examined the prevalence and the extent of coronary artery atherosclerosis in patients with systemic lupus erythematosus (SLE) using electron beam computed tomography.

Over a 34 month period 64 SLE patients and 69 age-, sex- and race-matched controls older than 18 years were enrolled. Subjects with a history of cardiovascular disease were excluded. Electron beam computed tomography was conducted on all subjects and all sites of coronary artery calcification were measured. Coronary artery atherosclerosis was defined as a calcified plaque which was the measurement of at least 3 consecutive pixels. Subsequently, the degree of coronary-artery calcification was estimated.

The following additional data were collected: current and cumulative medication dosage, medical history, family history of coronary artery disease (defined as a first-degree relative who had had a myocardial infarction or stroke prior to 55 years in first degree males or before 65 years in females), body-mass

index, blood pressure (hypertension was defined as systolic blood pressure of at least 140 or diastolic blood pressure of at least 90 mm Hg or the use of antihypertensive medication), disease activity (SLE Disease Activity Index - SLEDAI), damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index -SLICC), complete blood count, creatinine, total cholesterol, low-density lipoprotein cholesterol, triglycerides, Lp(a) lipoprotein by cholesterol content and homocysteine. In SLE patients, C-reactive protein, erythrocyte sedimentation rate, and total hemolytic complement were also measured. Results of ANA, anti-ds-DNA, anticardiolipin antibodies, and lupus anticoagulant were obtained from the medical records.

Mann-Whitney U tests and Fisher's exact tests were used to determine the distribution of coronary risk factors and calcium scores. Logistic regression model estimated independent associations between coronary-artery calcium and disease status after controlling for covariates.

Stein et al found that the patients and controls were comparable in terms of baseline characteristics including cardiovascular risk factors, except that hypertension, current smoking behavior, triglycerides, and homocysteine levels were significantly increased in SLE patients. Coronary artery calcification was much more prevalent in SLE patients (adjusted odds ratio 9.8, $P=0.001$). Three SLE patients had extensive coronary artery calcification as defined as score >400 , while none of the controls did. As compared to control subjects, SLE patients developed coronary artery calcification at younger age, and the prevalence increased with age. Calcification was present in 7% of SLE patients under 40 years of age, 35% of SLE patients and 15% of controls between ages 40-49 years, 78% of SLE patients and 21% of controls between ages 50-59 and 100% of patients with SLE and no controls in age group over 60 years. The absence of calcification in the >60 years age group is likely due to the small sample in that subgroup and repeating the analysis after excluding the subgroup did not change the results.

Stein et al found that SLE patients with and without coronary artery calcification were similar in most respects, including SLEDAI and SLICC scores,

except that older age ($P < 0.001$) and male gender ($P = 0.008$) were more common in those with calcification. Additionally, patients with calcification had higher average creatinine, and a lower frequency of anticardiolipin and anti-ds-DNA antibodies. However, the significance disappeared after adjustment for age and sex. The authors found no significant association between the presence of coronary artery calcification and the use of corticosteroid and/or hydroxychloroquine. Other immunosuppressive therapies were not considered.

Stein et al suggest that SLE patients have a higher prevalence of coronary atherosclerosis and develop it at a younger age. The study stresses the need for further research in young adults with SLE, early detection and close monitoring for development of coronary artery disease. Additionally, a larger sample may be needed to conduct exploratory analyses to examine the relationship of coronary artery atherosclerosis as demonstrated by this computer tomography with medication use, disease activity and damage.