



**Karolinska
Institutet**

Institution of Medicine, Department of Rheumatology

**Studies on cardiovascular risk factors in Systemic
Lupus Erythematosus**

AKADEMISK AVHANDLING

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av

Johanna Gustafsson

MD

Huvudhandledare:

Docent Elisabet Svenungsson
Karolinska Institutet
Institutionen för Medicin
Enheten för reumatologi

Bihandledare:

Forskarassistent Julia Simard
Karolinska Institutet
Institutionen för Medicin
Enheten för klinisk epidemiologi

Docent Kerstin Jensen-Urstad
Karolinska Institutet
Institutionen för klinisk forskning och
utbildning
Södersjukhuset

Fakultetsopponent:

Professor Sören Jacobsen
Kliniken för infektionssjukdomar och
reumatologi
Rikshospitalet
Köpenhamns Universitetssjukhus

Betygsnämnd:

Professor Hans Carlsten
Institutionen för medicin
Avdelningen för reumatologi och
inflammationsforskning
Sahlgrenska akademien
Göteborgs Universitet

Professor Karin Schenck-Gustafsson
Karolinska Institutet
Institutionen för medicin
Enheten för kardiologi

Professor Claes-Göran Östenson
Karolinska Institutet
Institutionen för molekylär medicin och
kirurgi
Enheten för endokrinologi och diabetes

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Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune, inflammatory disease that mainly affects women. The prognosis of SLE has improved dramatically, but mortality rates are still higher than in the general population. With the improved general prognosis, cardiovascular disease (CVD) has emerged as a major cause of morbidity and mortality among SLE patients. Previous studies have demonstrated that the development of atherosclerosis is accelerated in SLE, and have identified a set of traditional and non-traditional risk factors that characterize SLE patients with CVD. Nevertheless, many unsolved issues with respect to SLE related CVD remain. The general aim of this thesis was to investigate risk factors for manifest CVD and for cardiovascular mortality (CVM) in SLE, with special focus on traditional risk factors, lupus phenotype, inflammatory and endothelial biomarkers, autoantibodies and genetic predisposition.

In the first paper, we prospectively studied traditional and non-traditional risk factors for the development of the first cardiovascular event (CVE) in 182 SLE patients with a follow-up time of 8 years. 24(13%) patients had a first event. We demonstrated that of the traditional risk factors, only age and smoking predicted the first CVE. Additionally, antiphospholipid antibodies (aPL), endothelial biomarkers, represented by soluble vascular cell adhesion molecule 1 (sVCAM-1), and absence of thrombocytopenia were independent predictors of CVE. Thus, activation of the endothelium and the coagulation system are important features in SLE-related CVD and the importance to advocate smoking cessation among SLE patients is underscored.

In the second paper, we prospectively investigated causes of mortality and risk factors for overall mortality and CVM in a cohort of 208 SLE patients, with a follow-up time of 12 years. We also evaluated Systematic coronary risk evaluation (SCORE, tool for evaluating the 10 year risk for cardiovascular death in the age span 40-65 years, based on traditional risk factors) in this population. Cystatin C, a sensitive measure of renal function, in addition to traditional and non-traditional risk factors, were evaluated as risk factors. 42 patients died, 48 % of which were due to CVM. Age, previous arterial events and high cystatin C levels were the strongest predictors for overall mortality and for CVM. After adjusting for these three variables, smoking, sVCAM-1 and high sensitivity C-reactive protein (hsCRP) predicted CVM. SCORE estimated 4 but we observed 9 cases of CVM, a non-significant difference. We conclude that except for smoking, traditional risk factors are less important than cystatin C, endothelial and inflammatory biomarkers as predictors of CVM in SLE patients.

In the third paper, we investigated whether a risk allele for SLE in the signal transducer and activator of transcription factor 4 gene (*STAT4*) was associated with vascular events or presence of antiphospholipid antibodies (aPL). A total of 578 unrelated SLE patients (424 from mid-Sweden and 154 from southern-Sweden) were included in a cross-sectional design. Occurrence of previous cardiovascular events and aPL were tabulated. Matched controls (N=651) were genotyped as a comparison. The results demonstrate that the *STAT4* risk allele was associated with ischemic cerebrovascular disease (ICVD), with a dose-dependent relationship between ICVD and number of risk alleles. The risk allele was furthermore associated with the presence of two or more aPLs, also in a dose-dependent manner. The association remained after adjustment for known traditional risk factors. We conclude that patients with the *STAT4* risk allele have an increased risk of ICVD. Our results imply that genetic predisposition is an important risk factor for ICVD in SLE patients, and that aPL may be one underlying mechanism.

In the fourth paper, we evaluated the potential association between smoking and aPL. 367 SLE patients were investigated in a cross-sectional study. Occurrence of aPL (anticardiolipin (aCL) IgG and IgM, anti- β_2 glycoprotein-1 IgG ($\alpha\beta_2$ GPI IgG), lupus anticoagulant (LAC)) and smoking habits (never, ever, former, current) were tabulated. Never smoking was used as reference in all calculations. In multivariable models, adjusted for age, sex and age at disease onset, aCL and $\alpha\beta_2$ GPI of the IgG isotype and LAC were associated with ever smoking, this association seemed to be driven mainly by the former smoking group. Our results demonstrate that smoking is associated with pro-thrombotic aPL in SLE patients, though we can not from this study draw firm conclusions about the temporal relationship between exposure to smoking and occurrence of aPL. Further studies are warranted to investigate the mechanisms behind these observations.

In prospective studies we have demonstrated that in particular smoking, systemic inflammation, endothelial activation and aPL are major risk factors for SLE related CVD and CVM. Furthermore, genetic predisposition, in our studies represented by a *STAT4* SLE risk allele, contributes to the high risk of ICVD and to the occurrence of aPL, a possible underlying pathogenic mechanism. Finally we demonstrate that smoking, known to have unfavorable effects on the immune system and to significantly increase cardiovascular risk in SLE patients, is also associated with pro-thrombotic aPL in patients with SLE. Thus in SLE smoking stands out as the most important of the traditional risk factors with potential influence also on lupus related risk factors such as aPL.