Cutaneous lupus erythematosus and systemic lupus erythematosus are associated with clinically significant cardiovascular risk: a Danish nationwide cohort study

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Systemic lupus erythematosus (SLE) is a well-known cardiovascular risk factor. Less is known about cutaneous lupus erythematosus (CLE) and the risk of developing cardiovascular disease (CVD). Therefore, we investigated the risk of mortality and adverse cardiovascular events in patients diagnosed with SLE and CLE. We conducted a cohort study of the entire Danish population aged >18 and ≤100 years, followed from 1997 to 2011 by individual-level linkage of nationwide registries. Multivariable adjusted Cox regression models were used to estimate the hazard ratios (HRs) for a composite cardiovascular endpoint and all-cause mortality, for patients with SLE and CLE. A total of 3282 patients with CLE and 3747 patients with SLE were identified and compared with 5,513,739 controls. The overall HR for the composite CVD endpoint was 1.31 (95% CI 1.16–1.49) for CLE and 2.05 (95% CI 1.15–3.44) for SLE. The corresponding HRs for all-cause mortality were 1.32 (95% CI 1.20–1.45) for CLE and 2.21 (95% CI 2.03–2.41) for SLE. CLE and SLE were associated with a significantly increased risk of CVD and all-cause mortality. Local and chronic inflammation may be the driver of low-grade systemic inflammation. Lupus (2017) 26, 48–53.

Key words: Cardiovascular disease; cutaneous lupus; inflammation; lupus erythematosus; risk factor; systemic lupus erythematosus

Introduction

Lupus erythematosus (LE) is an inflammatory autoimmune disease divided into a systemic and a localized cutaneous form.1 The etiology of LE is multifactorial, where hormonal, genetic and environmental factors are regarded as important.2,3 Systemic lupus erythematosus (SLE) may involve organs such as the lungs, kidneys and heart, and 73–85% of patients with SLE show skin manifestations.4 Patients with primary cutaneous lupus erythematosus (CLE) may transit to SLE in about 10% of the cases.

Previous studies show that SLE patients have a 2–50-fold increase in the risk of developing cardiovascular disease (CVD).5–7 One of the reasons for this is chronic systemic inflammation, as described in previous studies as a risk factor for developing CVD,8–11 which is also seen in various inflammatory autoimmune diseases.12,13 By contrast, little is known about the CLE-related risk of CVD.13 Lessons from rheumatoid arthritis and psoriasis patients have taught us that such knowledge could have considerable impact; therefore, we used Danish nationwide registries of hospitalization, ambulatory visits and drugs dispensed from pharmacies to determine the risk of CVD in patients with SLE and with CLE, compared with the general population.

Materials and methods

Data sources and study population

The study was approved by the Danish Data Protection Agency. In Denmark, registry studies
are exempted from review of an ethics committee. The study comprised all Danish individuals aged \( \geq 18 \) and \( \leq 100 \) years of age from 1997–2011. The unique and lifelong personal registration number enabled us to link data at the individual level, from the following prospectively recorded registries:

1. Central Population Registry: Information on patient date of birth, gender and vital status were available;
2. National Patient Registry: Holds information on all in- or out-patient visits to Danish hospitals since 1978, with diagnoses according to the International Classification of Diseases (ICD) (prior to 1994, according to the 8th revision (ICD8) and thereafter, the 10th revision (ICD10)), which was used to obtain information on morbidity;
3. Finally, the Registry of Medicinal Product Statistics holds information on all prescription claims since 1995. All drugs are classified according to the Anatomical Therapeutical Chemical (ATC) classification. Pharmacies in Denmark are required to register all dispensed prescriptions. Data on death, comorbidity, concomitant medication and socioeconomic data were linked at the individual level.
4. Patients with LE were identified by their hospitalizations (in-patient or out-patient) for CLE (ICD-10: H011, L718, or L93) and SLE (ICD-10: M32). Patients with a history of CLE and/or SLE prior to the beginning of our study were excluded from the study. Likewise, subjects with a recent cardiovascular event (within 1 year of the study start date) were excluded.

Medical treatment and co-morbidity

The baseline (up to 6 months prior to inclusion) pharmacological treatment was identified by patient prescriptions (from the Danish Registry of Medicinal Product Statistics) for: platelet inhibitors (ATC classification code: B01AC), beta-blockers (C07), angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (C09), calcium antagonists (C08), loop diuretics (C03C), thiazide diuretics (C03A), oral anticoagulants (B01AA), spironolactone (C03D), cholesterol-lowering drugs (C10A), glucose-lowering drugs (A10), non-steroidal anti-inflammatory (NSAID) drugs (MA01A) and antidepressants (N06A). Baseline co-morbidity was defined by hospitalization (in the Danish National Patient Registry) up to 12 months prior to inclusion, according to the previously validated Charlson co-morbidity index. The co-morbidity index is the established sum for the 19 included clinical conditions, which were given weights ranging from one to six:

- 1: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes;
- 2: Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukemia, lymphoma;
- 3: Moderate or severe liver disease; and
- 6: Malignant tumor, metastasis, or acquired immunodeficiency syndrome (AIDS).

Outcomes

The primary study endpoint was a composite of cardiovascular death (ICD-10 I00-I99), myocardial infarction (ICD-10 I21 and I22), and stroke (ICD-10 I60, I61, I63 and I64). As a secondary endpoint, we examined all-cause mortality.

Statistical analysis

Patients were included on 1 January 1997 or on the subsequent day that the subjects reached 18 years of age, and were censored on 31 December 2011 or during follow-up, if an event or death occurred. Event rates per 1000 person-years and 95% CIs were calculated for patients with SLE, CLE and the reference population, respectively. Multivariable adjusted Cox regression models were used to estimate hazard ratios (HRs) and 95% CIs. We adjusted for confounding factors including age, calendar year, concomitant medication, comorbidity, socio-economic data and gender.

SLE and CLE status at a given age were included as time-dependent variables, to ensure accurate allocation of time at risk. Co-morbidity, use of medication and socioeconomic status were included as fixed variables obtained at baseline. Patient socioeconomic status was defined by the average yearly income in the 5 years preceding the beginning of the study, divided into quintiles. We created 1-year time bands and the patient’s age was updated at each time-band.

In addition, we repeated all analyses with inclusion of prescription drug use as a time-dependent variable, to ensure inclusion of continuously updated information on co-morbidities in the analyses. We repeated the main analyses with the exclusion of subjects with a prior cardiovascular
event (any date prior to study start) as well, to address the potential impact of pre-existing CVD. A 2-sided p-value < 0.05 was considered statistically significant. All analyses were performed with the use of SAS software (Version 9.2, SAS Institute, Cary, NC, USA), and Stata software (Version 11.0, StataCorp, College St., TX, USA).

**Results**

A total of 3282 patients with CLE and 3747 patients with SLE were identified in the Danish population from 1997 to 2011, and compared with 5,513,739 controls (Figure 1). The incidence rates of CLE and SLE were 3.96 and 4.52 per 100,000 persons/year, respectively.

The baseline characteristics of our study population are presented in Table 1. We found that the mean age was comparable between groups. Women were over-represented in the CLE and SLE group, i.e. they were 69.7% and 82.7% of the study population. We observed minor differences in baseline drug use and co-morbidity (Table 1).

CLE and SLE were associated with a significantly increased risk of CVD and all-cause mortality (Table 2). In the study period, 259 CLE patients and 315 SLE patients had composite CVD, compared with 540,839 controls. Likewise, the absolute events of all-cause mortality were 457 for the CLE patients, 566 for the SLE patients and 823,382 for the controls.

For both CLE and SLE, the risks of CVD and all-cause mortality were more pronounced in patients ≤ 50 years of age. In SLE patients in this age group, a composite CVD HR of 2.78 (95% CI, 1.15 to 3.44) was observed; compared to 1.78 (95% CI, 1.55 to 2.04) in those > 50 years of age. In patients ≤ 50 years of age with CLE, the composite CVD HR was 1.54 (95% CI, 1.18 to 2.00); compared to 1.25 (95% CI, 1.08 to 1.44) in CLE patients > 50 years of age.

The overall HRs for all-cause mortality were 1.32 (95% CI, 1.20 to 1.45) and 2.21 (95% CI, 2.03 to 2.41) for the CLE patients and SLE patients, respectively. For both groups of patients, the risk was higher in those patients ≤ 50 years.

**Sensitivity analyses**

The inclusion of prescription drug use as time-dependent information on co-morbidities in the

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**Figure 1** Flowchart of our selection of the study population.

analyses did not alter the results significantly. In the sensitivity analyses, the HR for the composite CVD endpoint for SLE patients was 1.91 (95% CI, 1.71 to 2.14), compared to 2.05 (95% CI, 1.83 to 2.30) in the main analyses; and in CLE patients, the HR was 1.27 (95% CI, 1.12 to 1.44), compared to 1.31 (95% CI, 1.16 to 1.49) in the main analyses. Likewise, the analyses having the exclusion of subjects with a prior cardiovascular event yielded comparable results (data not shown).

Discussion

In this Danish nationwide registry-based cohort study, CLE and SLE were significant
cardiovascular risk factors giving increased risks of stroke, acute myocardial infarction, cardiovascular death and all-cause mortality. Importantly, the study demonstrated an increased risk for CVD in CLE patients, including both in-patients and out-patients. The risk of having a composite CVD endpoint was 1.3-fold and 2-fold higher for CLE and SLE, respectively, compared to the general population in Denmark.

Chronic, systemic inflammation is described in previous studies as a risk factor for developing CVD. The reason for the increased risk of CVD in patients with SLE may be due to the chronic systemic inflammation. In addition SLE patients may have antiphospholipid syndrome, renal disease, hypertension and low levels of natural antibodies such as those against phosphorylcholine, which all are proven risk factors for developing CVD.

The pathogenesis underlying the association between CLE and CVD is less clear. Systemic inflammation is a likely link between these diseases, as seen in SLE and other inflammatory autoimmune diseases; however, little is known about the systemic markers of inflammation in patients with CLE. Stimulation by environmental triggers such as ultraviolet (UV) irradiation induces epidermal keratinocyte apoptosis, autoantigen externalization and alteration of cytokine chemo-kine production such as interferon (IFN), TNF-alpha, interleukin (IL)-1, IL-10 and IL-17, which may initiate a systemic inflammation. The above idea of increased local cytokine production and the following systemic leak could be an explanation of the association between local cutaneous inflammation and systemic inflammation resulting in CVD.

SLE, in the published literature, is a well-described cardiovascular risk factor and the risk of those patients having CVD is increased. In our study, the HR of the composite CVD endpoint was almost 3-fold higher in patients with SLE whom were ≤ 50 years of age, compared with the general population. Other population-based studies show the same 2–3-fold increased occurrence of CVD in unselected SLE cohorts.

A Swedish study examined whether there was an association between hospital admission for CLE and subsequent risk of hospitalization for coronary heart disease. The risk was greatest 1–5 years after being hospitalized with CLE (standardized incidence ratio (SIR) 2.38; 95% CI 1.67–3.30) and overall, the risk was almost doubled (SIR 1.86; 95% CI 1.55–2.21). The study was limited by low numbers of participants with CLE and it only included hospitalized CLE patients; hence, it might not represent the risk of developing coronary heart disease for all CLE patients, as most patients with CLE are not hospitalized.

Limitations and strengths

The present study does have certain limitations. We had no data on traditional cardiovascular risk factors such as body mass index (BMI), diet and smoking. Previous studies have shown that SLE patients smoke more than the general population and we cannot refute residual confounding. Information on smoking is not available in the databases; however, we indirectly adjusted for smoking using socioeconomic income and via chronic obstructive pulmonary disease.

Another limitation is that some CLE patients are followed by their private dermatologist or general practitioner, and our results cannot be generalized to these patients. It is most likely that they have a lower risk of CVD than the patients under hospital care, as they most likely are mild cases. Misclassification of patients with CLE as references would tend to bias the results towards having no differences in risk of CVD. Importantly, the impact of misclassification is likely minor, due to the very large sample size. Moreover, this limitation should not be present in patients with SLE, because in Denmark they are traditionally followed at a hospital.

The diagnoses of CLE and SLE in the Danish National Patient Registry have not previously been validated. Importantly, we found incidence rates of 3.96 and 4.52 per 100,000 persons/year for CLE and SLE, respectively. This is in line with previous findings and supports the methods used. Along this line, previous studies have shown that the diagnoses of myocardial infarction and stroke in the Danish registries are accurate. Most of the cohort data was previously used in another study, and here the CVD data was sought after. Finally, the Danish population is predominantly of Caucasian descent, and extrapolation of results to patients of other ethnicities should be carried out with caution.

The large number of participants, the nationwide coverage of recorded registries, no loss to follow-up and the long duration of the follow-up period represent major strengths. The nationwide coverage minimized selection bias, compared to data obtained from highly specialized centers. Also, the use of nationwide, prospectively recorded registries eliminated recall bias. Finally, the results were supported by the sensitivity analyses accounting for pre-existing CVD and changes in co-morbidities during follow-up.
Conclusions

CLE and SLE were significant cardiovascular risk factors with an increased risk of stroke, myocardial infarction, cardiovascular death and all-cause mortality. These results call for an increased awareness of the association between LE and cardiovascular morbidity and mortality. Further studies are needed to investigate the pathogenesis and the clinical relevance of the association between CLE and an increased risk of CVD.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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