Usage of drugs for cardiovascular diseases is increased in systemic lupus erythematosus (SLE) patients already before diagnosis of SLE

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Abstract

Objective

Systemic lupus erythematosus (SLE) patients are considered as a high-risk population for cardiovascular diseases (CVDs). To explore whether their risk is increased already in preclinical episodes of the disease, we have studied the usage of CVD drugs in incident SLE cases five years before diagnosis of SLE compared to the population controls.

Methods

Adult SLE incident patients (age ≥18 years) from 2004 through 2014 were identified from a nationwide register. The date of granted reimbursement for SLE medication was defined as the date of diagnosis (index day). For each patient, three population controls were matched for age, sex and residence on the index day. The patients and controls were linked to the drug purchase register. All purchases of CVD drugs (Anatomical Therapeutic Chemical (ATC) - codes of C01-C04, C07-C09) and separately C10 were recorded in half-year periods over five years before the index day.

Results

A total of 653 SLE patients (mean age 45.7±15.9 years, 83% females) and 1924 population controls were found. Over five years before the index day, the proportion of SLE patients with purchased CVD drugs (46.7%) was greater compared to the controls (28.5%) ($p<0.001$). The relative risk for purchases started to increase more steeply during the last half-year period before SLE diagnosis. There was no significant difference in lipid-modifying agents between groups.

Conclusion

Our finding that among SLE patients the use of CVD drugs was more common compared to their control population suggests increased CVD risk already before the diagnosis of SLE.

Key words

systemic lupus erythematosus, comorbidity, cardiovascular disease, connective tissue disease, register

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Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease, in which the likelihood of future cardiovascular disease (CVD) is higher than in the general population (1). In addition to traditional risk factors for CVDs, the disease-related factors like antibodies against endothelium, inflammation and robust atherosclerosis have central roles in the process (2). SLE and atherosclerosis also share similarities in their pathogenesis (3), which raises a question if atherosclerosis is a feature of disease itself rather than a distinct comorbidity.

It is well-documented that CVDs and CVD- related mortality in SLE are already seen in early disease course (4-6). The early stages of the pathogenesis of SLE and atherosclerosis are under ongoing research which may offer potential therapy targets later on (7-9). Earlier studies have confirmed that the disease process in autoimmune diseases like SLE starts years before diagnosis (10). Possibly the process of accelerated atherosclerosis is also turned on the years preceding diagnosis as the rate of cardiovascular events is increased soon after SLE diagnosis.

Initially, we hypothesised that there is a relationship between prevalence of CVDs and the frequency of usage of CVD drugs. We have previously shown in the cohort of incident SLE patients from years 2000–2007 in Finland, that SLE patients used significantly more often drugs for CVDs within the first year after diagnosis (11). Now the objective of the study was to find out if the purchases of cardiovascular medicines differed from the population controls already before SLE diagnosis.

Material and methods

The study took advantage of the register of new special reimbursements for drug cost in SLE between the years 2004 and 2014 and the drug purchase register, both maintained by the Social Insurance Institution (SII) of Finland. The patient identification method and reimbursement protocol are explained in detail in the earlier study (11). The study concentrated on adult patients (age ≥18 years). For each incident SLE patient, three controls individually matched with regard to age, gender, and place of residence were randomly selected from the Population Register Centre. Twenty-two of the controls were excluded due to concomitant rheumatoid arthritis diagnosis. The dates (month and year) when the decision regarding the special refund for anti-rheumatic drugs took effect was used as a proxy indicator of the date of SLE diagnosis, which is the index date in this study.

For SLE patients and their controls, purchases of drugs of cardiovascular system were observed in half-year periods over five years before the index date. These drugs were selected from the drug purchase register by their Anatomical Therapeutic Chemical (ATC) – classification system codes and the selected categories were as follows: C01 cardiac therapy, C02 antihypertensives, C03 diuretics, C04 peripheral vasodilators, C07 beta-blocking agents, C08 calcium channel blockers, C09 agents acting on the renin-angiotensin system and C10 lipid-modifying agents. Purchase of the selected drug at least once was interpreted as a sign of pathology of a disease that needed to be treated. Whether the patient sustained on the purchased drug could not be confirmed. This study was performed in accordance with the Regional Medical and Health Research Ethics regulations and as the study used only unidentifiable, encrypted patient data, there was no need for ethical approval. The data permit was received from the SII (74/522/2013).

Statistical methods

Time-to-event analysis was based on the product limit estimate (Kaplan-Meier) of the cumulative survival function. Relative risk (RR) and 95% confidence intervals (CI) were calculated using generalised linear models with appropriate distribution and link function. Stata 15.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

Results

A total of 653 adult SLE patients (540 females) and 1924 population controls were identified between the years

Table I. The proportions of purchasers of CVD drugs and their relative risks among incident SLE patients (diagnosed 2004-2014) within whole five-year period prior to SLE diagnosis compared to age-, gender-, and residence-matched population controls in Finland.

Drug category	ATC-code	Controls n=1924 (%)	Patients n=653 (%)	RR (CI 95%)	*p*-value
Cardiac therapy	C01	126 (6.5)	62 (9.5)	1.50 (1.09 to 2.06)	0.012
Anti-hypertensives	C02	10 (0.5)	13 (2.0)	3.89 (1.70 to 8.91)	0.001
Diuretics	C03	173 (9.0)	103 (15.8)	1.90 (1.46 to 2.46)	<0.001
Peripheral vasodilators	C04	4 (0.2)	-	-	0.244
Beta-blocking agents	C07	325 (16.9)	176 (27.0)	1.82 (1.47 to 2.24)	<0.001
Calcium channel blockers	C08	148 (7.7)	125 (19.1)	2.84 (2.20 to 3.67)	<0.001
Agents acting on the renin-angiotensin system	C09	261 (13.6)	160 (24.5)	2.07 (1.66 to 2.58)	<0.001
Drugs for cardiovascular system	C01-C09	549 (28.5)	306 (46.7)	2.21 (1.84 to 2.65)	<0.001
Lipid-modifying agents	C10	259 (13.5)	88 (13.5)	1.00 (0.77 to 1.30)	0.992

ATC: anatomic therapeutic chemical; SLE: systemic lupus erythematosus; CVD: cardiovascular disease; n: number; % percentage; RR: relative risk.

2004–2014 in Finland. Mean age at diagnosis was 45.3±15.7 years for females and 48.2±15.9 years for males.

The proportion of SLE patients with purchased CVD drugs (46.7%) was greater compared to their population controls (28.5%) (p<0.001) (Table I). Among SLE patients, there was no significant difference in purchases of drugs between genders. SLE patients had purchased higher proportions of CVD drugs almost in all selected ATC-code categories (C01-C03 and C07-C09) compared to controls. The highest RRs were in calcium channel blockers and agents acting on the renin-angiotensin system. There was no significant difference in purchases of lipid-modifying agents between the groups. Also, SLE patients did not have any purchases of peripheral vasodilators prior to diagnosis (ATC- code C04).

Figure 1 illustrates the difference in purchases of CVD drugs in SLE patients in half-year periods over five years before index day and in age-, gender- and residence-matched controls. The right image shows the RR for purchases of CVD drugs over 5 years before SLE diagnosis in SLE patients. The RR for purchases started to increase further half a year before SLE diagnosis.

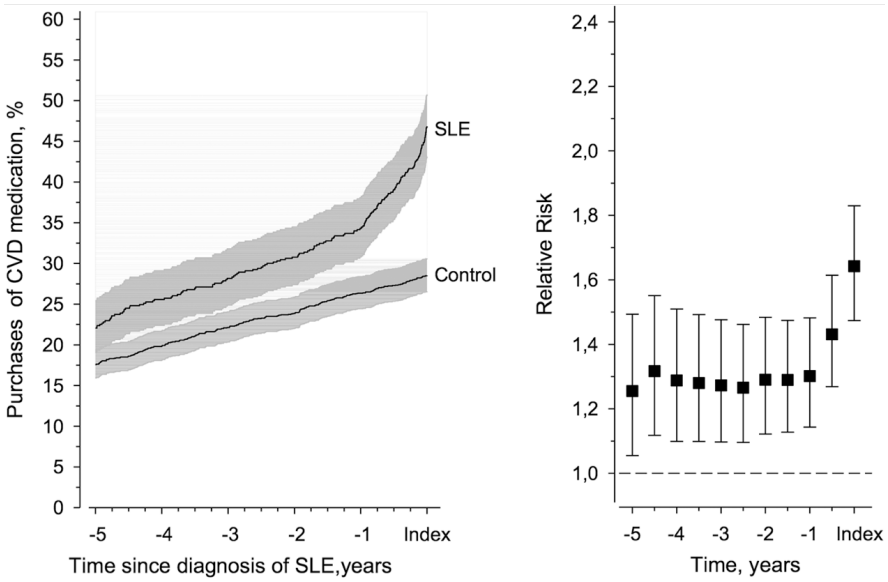

Fig. 1. Purchases of cardiovascular disease (CVD) drugs over 5 years before systemic lupus erythematosus (SLE) diagnosis in SLE patients and in age-, gender- and residence-matched controls (left image) and relative risk for purchases of CVD drugs in SLE patients in half-year periods 5 years before SLE diagnosis (right image). Lipid-modifying agents are not included into CVD medication in this figure. Grey areas illustrate 95% confidence intervals.

Discussion

The key finding of this nationwide study is that among SLE patients the use of CVD drugs was more common compared to the population controls already 5 years before the SLE diagnosis. This finding suggests that SLE patients have an increased risk for CVDs already before the diagnosis of SLE is confirmed. Interestingly, the difference was not seen in the purchases of lipid-lowering agents before diagnosis.

When comparing the present results to the earlier data on CVDs in SLE with different study methods, many similarities can be seen in the latest studies. A Canadian, population-based study analysed the hazard of CVDs in 4 863 early SLE patients compared to 49 316 population controls in the years 1996–2010. Within the first year of diagnosis, the overall risk for myocardial infarction (MI), stroke and CVD was six times higher in SLE patients than in controls. Although the hazard for future CVD stayed high at least five years since diagnosis, it was the highest during the first year of the disease. In that study, the increased risk was not related to traditional risk factors (4).

In the systemic lupus international collaborating clinics (SLICC) atherosclerosis inception cohort study (2000–2014) 1 848 patients were followed almost nine years since study entry. Altogether 31 patients experienced MI during follow-up. Seven of them had it in the two years after disease onset and 16 subjects beforehand, approximately 6 years preceding diagnosis. The occurrence of MI in the age group of 40–49 year-old patients was compared to self-reported MIs of the study population in Canadian Community Health Survey in Ontario in the same age group. SLE

patients (4.8%) suffered from MI more often than controls (0.7%) The main things behind the excess risk for MI were smoking, hypercholesterolaemia, hypertension and age (12).

Likewise, Bartels *et al*. have shown in a retrospective population-based study from north-central Wisconsin that 70 incident SLE patients from years 1991–2008 got almost four times (odds ratio: 3.8) more often CVD than 2 565 population controls within 2 years prior to SLE diagnosis (6). All these previously mentioned studies confirm that in the early SLE patients – prior or soon after the diagnosis – the likelihood of future cardiovascular events is substantially elevated, possibly due to accelerated atherosclerosis (4, 6, 12). Although the present study approached the CVDs indirectly through the evaluation of purchased CVD drugs, the message is still the same.

This raises a question on how to identify the individuals at a greater risk for CVDs. There is a growing body of evidence that SLE patients have an early, accelerated, subclinical atherosclerosis (13, 14). It has been reported that vascular stiffness and endothelial dysfunction display asymptomatic atherosclerosis and these can be measured by imaging techniques like B or M- mode ultrasound by determining carotid intima-media thickness (IMT) and carotid plaques (15, 16). However, this is not possible at the population level. In the Finnish Current Care Guidelines for treating dyslipidaemia, the target levels for low density lipoprotein (LDL) cholesterol differ according to the evaluated CVD risk (17). The higher risk could not be recognised in our future SLE patients. This may explain why lipid-lowering agents were not prescribed more often. It is also known that LDL alone does not reflect the risk of atherosclerosis in SLE that well (18, 19). There has been substantial research on the role of active disease and alterations of lipid levels and profile on accelerated atherosclerosis (20-22). It has been demonstrated that early active disease is related to higher levels of triglycerides and very low-density lipoprotein (VLDL) – cholesterol and lower levels of high-density lipoprotein (HDL) – cholesterol (21). Also, HDL in SLE patients seems to have pro-inflammatory properties (22).

Instead, high blood pressure and symptomatic coronary artery disease are more easily to recognise. The broader use of CVD drugs was clearly seen in the present study in SLE patients *versus* controls during the whole five years of observation. The role of hypertension in atherosclerosis in SLE patients is two-sided. High blood pressure is one of the most important traditional risk factors for CVDs and atherosclerosis partly due to endothelial damage it causes into vessels in various ways (23-25). In SLE, hypertension can also be related to lupus nephritis (24, 26). On the other hand, high mean blood pressure has been shown to be one of the best indicators of arterial stiffness, which again reflects subclinical atherosclerosis (27). Hence, hypertension is a risk factor and a sign for atherosclerosis.

In the present study, purchases of CVD drugs started to increase more rapidly half a year preceding the clinical diagnosis. One possible explanation is expanding inflammation, which has been found to stimulate atherosclerosis and thereby exacerbate CVDs. Previous data have shown that SLE-related risk factors for CVDs influence especially on early phases of atherosclerosis (16, 28). Instead, traditional Framingham risk factors like high blood pressure, dyslipidaemia, diabetes and body mass index have a more prominent role in the long run (28). Hypertension, diabetes mellitus, lower levels of HDL and higher levels of LDL have been more frequent in SLE patients (29). A recent Swedish study reported a higher incidence of MI in those SLE patients who smoked at diagnosis and a higher incidence of both MI and cerebrovascular event in those patients who were hypertensive at the time of SLE diagnosis (30).

In addition, early acceleration of CVDs is seen typically in those patients contracting SLE at an older age (6, 31), which is not uncommon in Nordic countries (11, 32). In this study, the mean age at diagnosis of SLE was 46 years.

The strength of the present study is that it uses nationwide and reliable register data. The comparison to the general population is comprehensive as it includes all permanent residents in Finland available for population controls. One limitation of this study is that we do not have data on what indications the CVD drugs were originally prescribed. The higher proportion of purchases of calcium channel blockers in SLE patients could be theoretically explained by the Raynaud's phenomenon. Nevertheless, even higher proportions of SLE patients purchased beta-blockers than calcium channel blockers. Secondly, as the study is register-based, it lacks clinical data. Thus, it was not possible to evaluate disease activity at baseline or delay to diagnosis. However, it is likely that immunological changes of disease were present years before diagnosis.

Based on results of the present study and previous reports, the risk of CVDs starts to increase already in early SLE disease. In future studies, it would be worthwhile to concentrate on the role of hypertension in atherosclerosis in early SLE patients in a prospective setting. In clinics, the high likelihood for future CVDs in early SLE patients deserves more attention to prevention immediately after the diagnosis of SLE is confirmed.

References

1. SHOENFELD SR, KASTURI S, COSTENBADER KH: The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: A systematic review. *Semin Arthritis Rheum* 2013; 43: 77-95.
2. KAHLENBERG JM, KAPLAN MJ: The interplay of inflammation and cardiovascular disease in systemic lupus erythematosus. *Arthritis Res Ther* 2011; 13: 203.
3. LEWANDOWSKI LB, KAPLAN MJ: Update on cardiovascular disease in lupus. *Curr Opin Rheumatol* 2016; 28: 468-76.
4. AVINA-ZUBIETA AJ, TO F, VOSTRETSOVA K, DE VERA M, SAYRE EC, ESDAILE JM: Risk of myocardial infarction and stroke in newly diagnosed systemic lupus erythematosus: a general population-based study. *Arthritis Care Res* 2017; 69: 849-56.
5. NOSSENT J, CIKES N, KISS E *et al*.: Current causes of death in systemic lupus erythematosus in Europe, 2000-2004: relation to disease activity and damage accrual. *Lupus* 2007; 16: 309-17.
6. BARTELS CM, BUHR KA, GOLDBERG JW *et al*.: Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. *J Rheumatol* 2017; 41: 680-7.
7. WOO JM, LIN Z, NAVAB M *et al*.: Treatment with apolipoprotein A-1 mimetic peptide

reduces lupus-like manifestations in a murine lupus model of accelerated atherosclerosis. *Arthritis Res Ther* 2010; 12: R93.
8. GENG L, WANG S, LI X, WANG D *et al*.: Association between Type I interferon and depletion and dysfunction of endothelial progenitor cells in C57BL/6 mice deficient in both apolipoprotein E and Fas ligand. *Curr Res Transl Med* 2018; 66: 71-82.
9. SANJADI M, REZVANIE SICHANIE Z, TOTONCHI H, KARAMI J, REZAEI R, ASLANI S: Atherosclerosis and autoimmunity: a growing relationship. *Int J Rheum Dis* 2018; 21: 908-21.
10. DORIA A, ZEN M, CANOVA M *et al*.: SLE diagnosis and treatment: When early is early. *Autoimmunity Rev* 2010; 10: 55-60.
11. ELFVING P, PUOLAKKA K, KAUTIAINEN H, VIRTA LJ, POHJOLAINEN T, KAIPIAINEN-SEPPÄNEN O: Drugs used in incident systemic lupus erythematosus – results from the Finnish nationwide register 2000-2007. *Lupus* 2016; 25: 666-70.
12. UROWITZ MB, GLADMAN DD, ANDERSON NM *et al*.: Cardiovascular events prior to or early after diagnosis of systemic lupus erythematosus in the systemic lupus international collaborating clinics cohort. *Lupus Sci Med* 2016; 3: e000143.
13. TARABORELLI M, SCIATTI E, BONADEI I *et al*.: Endothelial dysfunction in early systemic lupus erythematosus patients and controls without previous cardiovascular events. *Arthritis Care Res* 2018; 70: 1277-83.
14. LIU Y, KAPLAN MJ: Cardiovascular disease in systemic lupus erythematosus: an update. *Curr Opin Rheumatol* 2018; 30: 441-8.
15. WU GC, LIU HR, LENG RX *et al*.: Subclinical atherosclerosis in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmun Rev* 2016; 15: 22-37.
16. ZARDI EM, AFELTRA A: Endothelial dysfunction and vascular stiffness in systemic lupus erythematosus: Are they early markers of subclinical atherosclerosis? *Autoimmun Rev* 2010; 9: 684-6.
17. WORKING GROUP SET UP BY THE FINNISH MEDICAL SOCIETY DUODECIM, FINNISH SOCIETY OF INTERNAL MEDICINE: Finnish Current Care Guidelines , Dyslipidaemias. The Finnish Medical Society Duodecim. http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50025. Accessed 10 November 2019.
18. HUA X, SU J, SVENUNGSSON E *et al*.: Dyslipidaemia and lipoprotein pattern in systemic lupus erythematosus (SLE) and SLE- related cardiovascular disease. *Scand J Rheumatol* 2009; 38: 184-9.
19. BORBA EF, BONFÀ E: Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. *Lupus* 1997; 6: 533-9.
20. CROCA S, RAHMAN A: Atherosclerosis in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2017; 31: 364-72.
21. ZHOU B, XIA Y, SHE J: Dysregulated serum lipid profile and its correlation to disease activity in young female adults diagnosed with systemic lupus erythematosus: a cross-sectional study. *Lipids Health Dis* 2020; 19: 40.
22. KIM SY, YU M, MORIN EE, KANG J, KAPLAM MJ, SCHWENDEMAN A: High-density lipoprotein in lupus: disease biomarkers and potential therapeutic strategy. *Arthritis Rheumatol* 2020; 72: 20-30.
23. TAYLOR EB, RYAN MJ: Understanding mechanisms of hypertension in systemic lupus erythematosus. *Ther Adv Cardiovasc Dis* 2017; 11: 20-32.
24. MUNGUIA-REALPOZO P, MENDOZA-PINTO C, SIERRA BENITO C *et al*.: Systemic lupus erythematosus and hypertension. *Autoimmun Rev* 2019; 10: 102371.
25. SIGNORINI V, ELEFANTE E, ZUCCHI D, TRENTIN F, BORTOLUZZI A, TANI C: One year in review 2020: systemic lupus erythematosus. *Clin Exp Rheumatol* 2020; 38: 595-601.
26. CHAIAMNUAY S, BERTOLI AM, ROSEMAN JM *et al*.: African-American and Hispanic ethnicities, renal involvement and obesity predispose to hypertension in systemic lupus erythematosus: results from LUMINA, a multiethnic cohort (LUMINA XLV). *Ann Rheum Dis* 2007; 66: 618-22.
27. ČYPIENE A, DADONIENE J, MILTINIENE D *et al*.: The fact not to ignore: Mean blood pressure is the main predictor of increased arterial stiffness in patients with systemic rheumatic diseases. *Adv Med Sci* 2017; 62: 223-9.
28. TSELIOS K, GLADMAN DD, SU J, ACE O, UROWITZ MB: Evolution of risk factors for atherosclerotic cardiovascular events in systemic lupus erythematosus: A longterm prospective study. *J Rheumatol* 2017; 44: 1841-9.
29. YANG L, TAO J, TANG X *et al*.: Prevalence and correlation of conventional and lupus specific risk factors for cardiovascular disease in Chinese systemic lupus erythematosus patients. *J Eur Acad Dermatol Venereol* 2012; 26: 95-101.
30. NIVED O, INVARSSON RF, JÖUD A *et al*.: Disease duration, age at diagnosis and organ damage are important factors for cardiovascular disease in SLE. *Lupus Sci Med* 2020; 7: e000398.
31. MANZI S, MEILAHN EN, RAIRIE JE *et al*.: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: a comparison with the Framingham study. *Am J Epidemiol* 1997; 145: 408-15.
32. INGVARSSON RF, BENGTSSON AA, JÖNSEN A: Variations in the epidemiology of systemic lupus erythematosus in southern Sweden. *Lupus* 2016; 26: 772-80.