EXTENDED REPORT

Factors associated with coronary artery calcification in young female patients with SLE

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Background: With improved survival rates of patients with systemic lupus erythematosus (SLE), damage such as accelerated atherosclerosis gains increasing importance.
Objective: To identify the prevalence of coronary artery calcifications (CAC) in asymptomatic patients.
Methods: Electron beam tomography (EBT) was performed in 75 female patients with SLE aged <50. The results were correlated with traditional and SLE related factors associated with CAC. 49 women with symptomatic coronary heart disease (CHD) and 279 women without CHD were also analysed.
Results: Overall, 21/75 (28%) patients had CAC. Low HDL cholesterol levels <1.40 mmol/l (p=0.03, OR=1.8, 67% *v* 39%) and cigarette smoking (p=0.01, OR=5.7, 76% *v* 44%) were identified as factors associated with CAC. Hypertension and high cholesterol were more common in women with CHD (p<0.01) than in those without CHD. SLE related factors were proteinuria (1331 *v* 465 mg/day, p=0.02), impaired renal function (p=0.02, OR=2.6, 26% *v* 6%), and high C3 levels (p=0.04, OR=1.8, 65% *v* 38%). High C3 levels were also more common in symptomatic CHD (p=0.02). The prevalence of Sm antibodies was lower in patients with CAC (15% *v* 42%, p=0.03). In a multivariate analysis, cigarette smoking, reduced renal function, high C3, and a cumulative steroid dose above 30 g were the most important CAC associated factors in the lupus cohort.
Conclusion: A subgroup of patients with SLE with CAC without any clinical symptoms of CHD was identified by EBT. Therefore, EBT is useful for assessing asymptomatic atherosclerosis in this group.

Systemic lupus erythematosus (SLE) is a prototype of an autoimmune disease with a broad spectrum of autoantibodies and clinical symptoms and still unknown aetiology. Mostly women of childbearing age are affected. Cardiovascular disease is common in SLE.[1] However, little is known about the prevalence of preclinical disease and associated factors. In the Erlangen cohort cardiovascular disease accounts for 37% of the deaths. Contributing factors may include traditional risk factors for coronary artery calcification (CAC), such as hypertension and hyperlipidaemia. However, the role of SLE related factors for the development of CAC is not known and the mechanism of accelerated atherosclerosis in SLE remain uncertain.

Electron beam tomography (EBT), a cross sectional imaging technique with high spatial and temporal resolution, permits the sensitive detection and quantification of coronary calcifications. Coronary calcium is closely associated with the presence and extent of atherosclerotic plaque and therefore constitutes a potential marker for early stages of coronary atherosclerosis in asymptomatic subjects.[2 3–6]

Manzi *et al* showed that coronary artery disease was more common among young women with SLE than among healthy women of the same age.[7] However, the prevalence of preclinical, asymptomatic CAC in young women with SLE is not known; few assessments of CAC have been performed in women with SLE aged <50, and there is no information about the risk profile for premature atherosclerosis in women aged <50 with preclinical atherosclerosis.

PATIENTS AND METHODS

Study group

Seventy five unrelated white women with SLE from the Erlangen cohort[8] aged <50, followed up at the Department of Medicine III, University Erlangen-Nuremberg, were randomly selected irrespective of their disease severity or stage of the disease. Twenty three patients were younger than 35 years, six were younger than 30 years. Forty nine of 328 female patients of the Erlangen lupus cohort have manifest coronary heart disease (CHD), and 13 women have had a myocardial infarction. Those patients were excluded from the EBT study, but data of this subgroup are included. Demographic data, including age and age at the time of first diagnosis, were obtained retrospectively from the official medical records at the time of the first visit until December 2000. Frequent clinical manifestations, haematological and immunological parameters, an activity score (European Consensus Lupus Activity Measurement (ECLAM)),[9] and a damage index (Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI))[10] were recorded at each visit, with a maximum of three visits a year.

All patients fulfilled the 1997 revised criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE.[11] Skin manifestations, including malar rash, discoid rash, photosensitivity, and oral ulcers were present in 82%, 41%, 84%, and 35% of our SLE cohort, respectively; arthritis was seen in 70%, serositis in 23%, nephritis in 53%, neurological disorder in 21%, haematological abnormalities in 88%, dsDNA antibodies in 96%, and antinuclear antibodies in 99% of our patients. The major organ involvements were defined according to the ACR criteria.[11] All abnormalities were recorded at

Abbreviations: ACR, American College of Rheumatology; BMI, body mass index; CAC, coronary artery calcification; CHD, coronary heart disease; CRP, C reactive protein; EBT, electron beam tomography; ECLAM, European Consensus Lupus Activity Measurement; HDL, high density lipoprotein; LDL, low density lipoprotein; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLE, systemic lupus erythematosus

Table 1 Characteristics of the study group

	All	Calcifications +	Calcifications –
All patients with SLE (n)	75	21	54
Median age at SLE diagnosis (y)	27.0 (14-27)	29.1 (16-38)	25.9 (14-39)
Median age at EBT (y)	38.8 (20-48)	41.0* (28-48)	37.0 (20-48)
Median disease duration (y)	10.1 (0.04-21)	13.1 (0.3-21)	9.3 (0.04-20)
Median ECLAM score	3.1 (0.4-6)	3.1 (0.4-6)	3.0 (1.8-4.4)
Median SDI, year 5	1 (0-6)	1 (0-6)	1 (0-5)

*p=0.02

the time of the first appearance either under our care or from a well documented history and for the whole follow up period. Patients had no clinical signs of CHD, documented by a regular history, electrocardiogram without signs of CHD, and echocardiography without structural or functional signs of CHD. As *x* ray exposure was necessary, a control group was considered not ethical.

Screening for CAC was performed by EBT. Before the scan, single measurements of serum chemistry, including total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL), triglycerides, homocysteine, Lp(a) lipoprotein, and C reactive protein (CRP) were collected. In addition, traditional risk factors such as smoking habits, diabetes, hypertension, family history were assessed using a questionnaire. Height and weight were measured to calculate body mass index (BMI). In addition, a pregnancy test was performed before the scan. The study was approved by the local ethics committee.

Protocol for electron beam tomography

All EBT scans were performed with a C-150XP electron beam tomography scanner (Imatron Inc, South San Francisco, CA) according to a standard protocol.[4] The scanner's high resolution, single slice mode with 3 mm slice thickness and an acquisition time of 100 ms per image was used, and 40 consecutive axial cross sections of the heart were acquired in inspiratory breathhold, triggered to the electrocardiogram at 40% of the R wave to R wave interval. For evaluation, images were transferred to an offline workstation. Coronary calcium was assumed to be present if a computed tomography attenuation value of at least 130 HU was found in two or more adjacent pixels which could be assigned to the coronary artery system. Semiautomated software was used to calculate the "Agatston score" after manual identification of calcified lesions in the coronary arteries. The Agatston score is a quantitative measure of the extent of coronary calcification which takes into account the area and density of calcified plaques.[4]

Statistical analyses

Data were analysed with the statistics package SPSS 10.0 for Windows. To test the null hypothesis that categorial variables such as clinical and serological parameters are equally distributed between patients with and without CAC, a two tailed Pearson's χ^2 test was applied. The strength of the association of certain clinical or serological markers of SLE, of disease activity and chronicity, with the frequency of CAC was estimated by the calculation of odds ratios.[12] Median and range were calculated for age at diagnosis, ECLAM score, and SDI because no parametric distribution can be assumed for these data. Mann-Whitney tests were used to test for the null hypothesis that these parameters do not differ between patients with and without CAC. A p value <0.05 was considered significant. Finally, multiple logistic regression models were performed[13] to define the possible role of clinical and/or laboratory features, treatments, activity or chronicity as factors associated with CAC. All analyses were adjusted for age at disease onset and age at EBT by defining categorial variables. In these models, a p value $=0.1$ was considered significant.

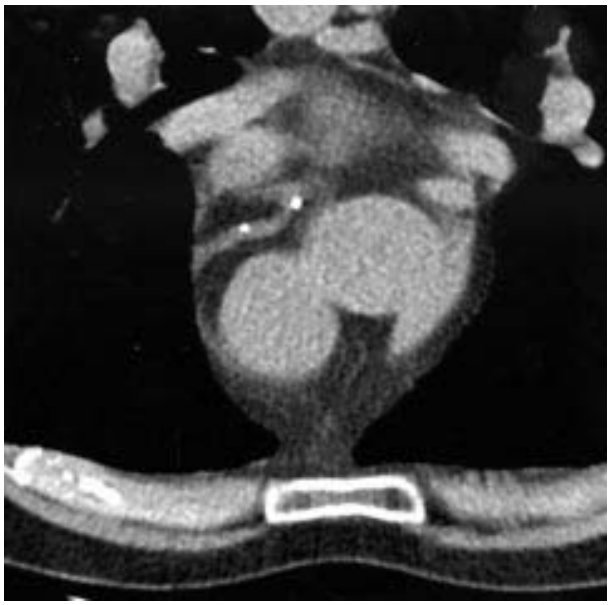

Figure 1 CAC in a woman with SLE, demonstrated by EBT. Coronary calcium (visible as white spots) is closely associated with the presence and extent of atherosclerotic plaques.

RESULTS

The median age of the 75 women who underwent screening for CAC was 38.8 years (range 20–48). Their median disease duration was 10.1 years. On average, the patients with CAC were older (41 *v* 37 years, p=0.02) and had a longer disease duration (13.1 *v* 9.3 years, p=0.08) (table 1). Among the six patients younger than 30 years, one had evidence of CAC. In contrast, 20/69 (29%) patients older than 30 and 18/52 (35%) older than 35 years had evidence of CAC. In the whole EBT cohort without clinical signs of CHD, 21/75 (28%) had evidence of CAC (fig 1). For disease activity and damage, measured by the ECLAM score and the SDI, we could not find a significant difference between patients with SLE with and without CAC (table 1) and with and without symptomatic CHD. Forty nine female patients with SLE with symptomatic CHD were older at lupus diagnosis ($p<0.01$) than the 279 female lupus patients without CHD and showed no significant difference in median ECLAM score and SDI at year 5 (table 1).

Sixteen of 21 (76%) patients with CAC were smokers as compared with 24/54 (44%) in the group without CAC (p=0.01). Low HDL was present in 14 (67%) patients with and in 21/54 (39%) patients without CAC (p=0.03). Also, raised levels of cholesterol, LDL, triglycerides, Lp(a) lipoprotein, and hypertension were found more commonly in women with CAC without reaching statistical significance. No differences were seen in family history, BMI, level of homocysteine, and diabetes (table 2). In 49 women with symptomatic CHD, hypertension and high cholesterol levels were more common than in women without CHD ($p<0.01$). Other traditional risk factors are not registered in the database.

Table 2 Traditional CAC associated factors in women with SLE, aged <50 with and without calcifications. Results are given as percentages

	Calcifications + (n=21)	Calcifications – (n=54)
Positive family history	14	13
Body mass index ⩾27	29	28
Hypertension	33	24
Cigarette smoking	76**	44
Diabetes	5	4
Menopausal status	29	15
Homocysteine >15 mmol/l	10	13
Hyperlipidaemia	33	19
Cholesterol >4.90 mmol/l	60	50
HDL <1.40 mmol/l	67*	39
LDL >3.90 mmol/l	29	19
Triglycerides >2.26 mmol/l	16	11
Lp(a) lipoprotein >0.8 mmol/l	20	19

*p=0.03; **p=0.01.

Table 3 Renal function and proteinuria in women with SLE, aged under 50 with or without calcifications

	Calcifications +	Calcifications –
Creatinine >110 µmol/l (%)	26*	6
Maximum creatinine (µmol/l)¶	160	110
Maximum proteinuria (mg/day)¶	4893	1407
Mean proteinuria (mg/day)‡	1331*	465

*p=0.02; †p=0.06; ‡mean values over time, three measurements/year were included in the calculation; ¶mean of maximum of tested patients.

Table 4 CAC associated factors in women with SLE, aged under 50

	Calcifications (%)	OR¶ (p value)
All women	28.0	
CAC associated factors:		
Cigarette smoking*	40.0	3.8 (0.06)
Steroid intake >30 g†	33.3	2.3 (0.07)
Creatinine >110 µmol/l‡	62.5	16.4 (0.002)
C3 >0.9 g/l‡	41.9	4.0 (0.007)
Sm antibodies	13.0	0.26 (0.04)

Multiple logistic regression, adjusted for age.
*Total numbers of packet years (median: 10 years (0.5–30)); †cumulative steroid intake over time; ‡mean values over time; measurements/year were included in the calculation; ¶OR= odds ratio.
After additional adjustment for disease duration p values are 0.006 (cigarette smoking), 0.1 (steroid intake >30 g), 0.05 (creatinine >110 µmol/l), 0.03 (C3 >0.9 g/l), 0.04 (Sm antibodies).

A reduced renal function was present in 6/21 (29%) patients with CAC as compared with 3/54 (6%) patients without CAC (p=0.02) and in 7/49 (14%) lupus patients with symptomatic CHD and 31/279 (11%) without CHD. Mean proteinuria was 1331 mg/day in patients with CAC compared with 465 mg/day in patients without CAC (p=0.02) (table 3). However, we could not find a significant difference in major organ involvements—for example, central nervous system disease, serositis, or vasculitis between patients with SLE with and without CAC and with and without symptomatic CHD.

Markers of active lupus such as dsDNA antibody titres >50 U/l (75% *v* 59.6%, NS) and markers of inflammation, such as high complement C3 (65% *v* 38%, p=0.04), raised fibrinogen (35% *v* 21%, NS), and CRP >50 mg/l (52% *v* 35%, NS) were more common in patients with CAC. Interestingly, high C3 was also more common in patients with symptomatic CHD (63% *v* 46%, p=0.02). Sm antibodies were present in 23/54 (43%) patients without CAC compared with 3/21 (14%) with CAC (p=0.03), but this difference could not be found in patients without (26%) and with (29%) symptomatic CHD. The frequency of other autoantibodies, including anti-phospholipid antibodies, did not vary significantly between both groups.

Because long term steroid intake may influence atherogenesis, we investigated the role of cumulative steroid intake for the development of CAC. The mean (SD) cumulative steroid intake was 31 939 (27 067) mg in patients with CAC compared with 20 270 (19 699) mg in patients without CAC (p=0.05).

In multivariate analyses adjusted for age, we identified cigarette smoking, cumulative steroid intake >30 g, reduced renal function, and high C3 as significant and the most important factors associated with the prevalence of CAC in women with SLE aged <50 without clinical signs of CHD (table 4). How the presence of Sm antibodies might exert a protective effect with respect to CAC, as shown in table 4, is still an open question.

DISCUSSION

Coronary events are rare in women under the age of 50,[14 15] except for women with familial hypercholesterolaemia,[16] premature menopause,[17] rheumatoid arthritis,[18] and SLE.[7 19 20] CHD is the leading cause of death among female patients with SLE.

EBT is a sensitive, non-invasive method for detecting CAC in patients without clinical signs of CHD who are at risk of developing clinically overt CHD, and for analysing their risk profile. Indeed only 10% of women between the age of 40 and 49 with normal renal function were reported to develop CAC.[21] In the EBT study of Hoff *et al* on 35 246 asymptomatic subjects[15] 1% of women aged <50 (n=3299) had CAC, whereas in our study 21/75 women with SLE (28%) who were younger than 50 had CAC. Keelan *et al* found that the extent of CAC shown by EBT is highly predictive of future serious cardiac events.[22] Several traditional risk factors for CHD in women older than 50, such as hypertension or hyperlipidaemia, did not show a strong association with CAC in the present study of young patients with SLE without clinical signs of CHD, although all traditional risk factors except for BMI, family history, and diabetes were more common in patients with CAC. Probably our negative results for some traditional risk factors are associated with the young age and sex of this cohort. Recently published data from Sweden comparing female lupus patients with and without CHD found no differences in disease duration, blood pressure, BMI, smoking, and diabetes between the groups.[23] In our female CHD cohort hypertension is more common than in those without CHD (p<0.01). Smokers were more frequently found in our lupus cohort with CAC, but the median age of our group was 38.8 compared with 52 years in the Swedish cohort. Traditional risk factors have been defined for both sexes, but effects may be different in women.[24] Diabetes has been described as a stronger risk factor for CHD in women than in men and is the most common cause for premature atherosclerosis[25] in women; this could not be confirmed in our young lupus cohort. With regard to the serum lipids, low HDL was associated with CAC in our patients with SLE and in the Swedish patients with CHD, whereas LDL concentrations did not differ between the groups. This may be influenced by the strong interrelationship between not only nephritis but also steroid treatment and lipid metabolism in lupus patients. We have not yet measured oxidised LDL in our cohort, but are planning to do that and to look for a correlation with CAC. Petri *et al* showed that oxidised LDL was

associated with carotid plaque (p=0.02) but not with coronary calcification. They found no correlation with anti-oxidised LDL.[26]

Steroid treatment is potentially atherogenic owing to its effects on plasma lipoproteins. The duration of treatment and the cumulative intake of corticosteroids was substantially higher in patients with CAC than in those without CAC. These data are in accordance with results from 52 Swedish patients with SLE and CHD, who also had a higher cumulative steroid intake than the control group.[23] Data from Svenungsson *et al*, who found higher levels of lupus anticoagulant and higher levels of CRP in symptomatic patients with SLE with CHD,[23] could not be confirmed in our group of patients with SLE with preclinical CHD, although CRP levels >50 mg/l (means over time) were present in 52% of patients with CAC compared with 35% of patients without CAC. Phospholipid antibodies seem to be associated to myocardial infarction but not with atherosclerosis. Our data on higher mean C3 levels in female patients with SLE with CAC and CHD are confirmed by recently published data of Selzer *et al*.[27] Renal damage is strongly associated with CAC in our cohort as well as in young adults with end stage renal disease undergoing dialysis.[28] Obviously, young patients with chronic renal failure have CHD that is not completely understood.[29 30]

Cardiovascular disease is the leading cause of death in the Erlangen lupus cohort, occurring in 37%. Our findings indicate that almost one third (28%) of young women with SLE have radiographic evidence of clinically silent and potentially serious CAC. Further studies are necessary to determine whether the described relation between CAC in EBT and angiographically documented coronary artery lesions in the general population is applicable to young women with SLE. Besides traditional risk factors, such as cigarette smoking, we were able to identify SLE related factors associated with accelerated atherosclerosis, such as reduced renal function, high steroid intake, and high C3. Within the group of young women with SLE, it is possible to identify a subgroup at risk for accelerated atherosclerosis. The most important limitations of this study are the lack of a control group and the lack of data on some traditional risk factors like LDL over time. All other data, such as creatinine, are not single measurements, but mean values over time, which may be very important, in view of the pathogenesis of atherosclerosis in this cohort. Owing to the *x* ray exposure of young healthy women needed, a control group was considered not ethical. Further studies need to elucidate whether the factors associated with SLE can predict CAC. Identification of patients, who may benefit from early and consequent therapeutic interventions, might lower cardiovascular mortality in women with SLE. This report provides information about preclinical coronary heart disease in women aged <50 in SLE, demonstrated by calcifications in EBT and CAC associated factors.

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