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Brief communication (Original)

Subclinical atherosclerosis in young Thai adults with juvenile-onset systemic lupus erythematosus

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Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in adult patients with systemic lupus erythematosus (SLE). Increased risk of CVD and atherosclerosis has been demonstrated in children with SLE. However, evidence of atherosclerosis in adults with juvenile-onset SLE is limited and their additional CVD risk factors unclear.

Objectives: To investigate the presence of subclinical atherosclerosis in young Thai adults with juvenile-onset SLE, and evaluate atherosclerotic risk factors.

Methods: We recruited a cohort of patients aged 18–40 years who had been diagnosed SLE before the age of 18 years for this observational study. Patients with chronic kidney disease stage IV or V, alcoholism, chronic liver disease, or life threatening illness were excluded. Common carotid intima-media thickness (CCIMT) was measured. Clinical and laboratory parameters, treatment, and SLE-related factors, which could be risk factors for atherosclerosis and classic risk factors were obtained.

Results: We enrolled 29 patients (24 female). Their mean age was 25.1 years and mean disease duration 11.3 years. The age of participants, persistent proteinuria and use of cyclosporin correlated with increased CCIMT by multivariable analysis ($P = 0.02$, 0.02, and 0.03, respectively). These patients had significantly abnormal CCIMT when compared with a healthy population (mean 690 (SD 150) μm versus mean 447 (SD 76) μm, respectively; $P < 0.001$).

Conclusions: Subclinical atherosclerosis, identified by abnormal CCIMT, appears in young adults with juvenile-onset SLE. The CCIMT abnormality progresses with increasing age, and persistent proteinuria and use of cyclosporin appears to increase the risk for atherosclerosis.

Keywords: Atherosclerosis, carotid intima-media thickness, juvenile-onset systemic lupus erythematosus, subclinical atherosclerosis, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a relapsing and remitting course of multisystem inflammation. Although the overall mortality in SLE has decreased during recent decades because of improvement in SLE management and novel medications for SLE, the mortality and morbidity from cardiovascular diseases (CVDs) remains unchanged or is increasing [1, 2]. Increased risk of myocardial infarction has been demonstrated in all age groups of study patients with SLE. This is particularly true in middle-aged women, with 50-fold increase compared with age-matched controls [3]. In juvenile-onset SLE, the patients have a 100–300-fold increased risk of death from CVD during early adulthood, compared with age-matched controls [4]. Hersh et al. [5] reported that patients with juvenile-onset SLE developed their first myocardial infarct at a much earlier mean age than subjects with adult-onset disease (32 years vs 48.1 years). Atherosclerosis, which is predictive of CVD, has been found in patients with SLE with approximately 2–4-fold increase compared with controls [6]. Although the prevalence of atherosclerosis in pediatric SLE is uncertain, increased evidence of subclinical atherosclerosis in children,

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documented by carotid intima-media thickening, has been reported [7-9]. Greater evidence of hypertension, dyslipidemia, and insulin resistance has also been reported in children with SLE than without [10-13]. High prevalence of atherosclerosis and CVD in patients with SLE cannot be explained by classic risk factors alone. The high prevalence of atherosclerosis and CVD is also attributable to multiple factors associated with the disease itself and the adverse effects of its usual treatment [6].

Our present study was designed to demonstrate the presence of carotid atherosclerosis, determined by measuring the common carotid intima-media thickness (CCIMT), and to evaluate the classic and SLE-related atherosclerotic risk factors in young Thai adults with juvenile-onset SLE.

Patients and methods

Study population

The study population was identified by International Statistical Classification of Diseases, 10th revision (ICD-10) code M32.1 in the Siriraj Hospital medical records unit. Patients were contacted by telephone to collect data and asked to participate voluntarily. Enrollment took place from August 2011 to August 2014. The eligible participants included patients who met the American College of Rheumatology (ACR) 1997 revised criteria for SLE before age of 18 and to age 40 and who had a disease duration longer than 2 years. Exclusion criteria were chronic kidney disease stage IV or V, alcoholism, chronic liver disease, or any other life threatening illness. All patients in the cohort provided written informed consent for their participation in this observational study. Ethical approval by our institutional review board was obtained (approval No. 439/2553) and the study was also approved by our Institutional Research Committee on November 26, 2010 (approval No. RO15432023).

Clinical and laboratory parameter measurement

Staff physicians collected clinical data variables from chart review, history taking, physical examination, and patient questionnaires assessing physical activities. CCIMT measurements, laboratory tests including urinalysis, complete blood count, serum creatinine, fasting blood glucose, insulin level, and lipid profile, high sensitivity C-reactive protein, erythrocyte sedimentation rate (ESR), anti-double stranded DNA antibody (anti-dsDNA), complement C_3, lupus anticoagulant and anti-cardiolipin antibodies were obtained on the same day. Classic risk factors for atherosclerosis, including hypertension, diabetes, insulin resistance, dyslipidemia, family history of premature coronary heart disease, smoking, lack of physical activity, and overweight, were assessed. Hypertension was defined as "persistent high blood pressure longer than for 3 months or the use of long-term antihypertensive agents". Diabetes was defined as "having fasting blood glucose of 126 mg/dL or more". Insulin resistance was defined as "a homeostasis model assessment index [insulin (U/mL) × (glucose (mg/dL)/405)] exceeding 4.1". Dyslipidemia was defined as "a fasting serum LDL cholesterol of ≥130 mg/dL, total cholesterol of ≥200 mg/dL, triglyceride of ≥150 mg/dL, HDL cholesterol of <40 mg/dL or the use of lipid lowering agents". Family history of premature coronary heart disease was defined as "participant-reported myocardial infarction or angina in parents or grandparents before the age of 55 years in men and 65 years in women". Physical activities were expressed by metabolic equivalent of task (MET) defined as "the ratio of metabolic rate during a specific physical activity to a standard resting metabolic rate". Physical activities of less than 3 METs were considered as a sedentary lifestyle [14, 15]. Body mass index of ≥23 was considered as overweight.

Laboratory test data indicating active SLE included leukopenia, lymphopenia, and thrombocytopenia according to the ACR criteria for SLE, elevated ESR, low complement C_3, positive anti-ds DNA and active urine sediment. Persistent proteinuria and hematuria referred to urine protein by dipstick of >1+ and 5 red blood cells/high power field, respectively, persisting for longer than 3 months. Impaired renal function was defined as "estimated glomerular filtration rate (eGFR) of less than 90 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation". Corticosteroid dosages, recorded as prednisolone equivalents, were disease duration-adjusted and expressed in mg/day. Cyclophosphamide and azathioprine dosages are expressed as cumulative dosage. Cyclosporin and tacrolimus use was defined as either previous or current use of the medication.

Measurements of CCIMT

Participants are placed in a supine position, the neck extended and turned contralaterally by about 45°. CCIMT, defined as the distance between the lumen-intima and media-adventitia borders of the common carotid artery, was evaluated using an iE33 xMATRIX

echocardiography system (Philips) with an L15-7io broadband compact linear array (7–15 MHz). The measurements were performed by a pediatric cardiologist who was blinded to the characteristics and laboratory test results of the participants. They were made on both common carotid arteries at the far proximal zone (about 1.5 cm from the flow-divider) and distal zone (about 0.5 cm from the flow-divider). Mean values of 4 readings in each participant were used for analyses.

Statistical analysis

The patient demographic, clinical, and laboratory test characteristics were summarized using descriptive statistics presented as mean with standard deviation or median with range for continuous variables and as percentages for categorical variables. Differences of CCIMT between levels of categorical variables were assessed with a 2-sample test or Mann–Whitney *U* test, as appropriate, with a 2-tailed $P < 0.05$ indicating significance. A simple linear regression model identified the relationship between each variable and CCIMT to select candidates for multiple linear regression. Variables with $P < 0.1$ were included in multivariable linear regression modeling. Several model-building procedures were used, including forward, backward, and stepwise regression, to produce a final model. $P < 0.05$ was considered to be significant. Statistical analyses were performed by using SPSS for Windows, version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

We identified 312 patients from the medical records system who met the ACR criteria for SLE before the age of 18 years, and were aged between 18 and 40 years at the beginning of the study. We were able to contact just 43 patients or their families. Of these, 5 patients had died, 3 patients had end stage kidney disease, 6 patients declined to participate, and 29 patients enrolled in the study. Demographic and clinical characteristics of the participants are shown in **Table 1**.

Differences in CCIMT, according to classic risk factors for atherosclerosis are shown in **Table 2**.

Almost all patients had a sedentary lifestyle. More than half had dyslipidemia. About one-third were overweight and had hypertension. None had diabetes or a history of smoking. There was a trend towards increased CCIMT in the participants with a sedentary lifestyle, dyslipidemia, overweight, and with hypertension, although differences were insignificant.

Seven participants (24%) had leukopenia and 15 (52%) had lymphopenia. The mean eGFR was 110.8 (range 56–137) mL/min/1.73 m^2. Among the participants with abnormally high lipid profiles, there was high a cholesterol level in 15 participants (52%), high triglyceride in 7 (24%), high LDL in 12 (41%), and low HDL in 3 (10%). Low complement C3 level and positive anti-dsDNA were demonstrated in 13 (45%) and 17 (59%) participants, respectively. In the immunosuppressed, 21 (72%) and 22 (76%) were either currently or previously receiving cyclophosphamide and azathioprine. All participants received corticosteroid with average dose of prednisolone equivalents of 9.4 (range 2.6–27.5) mg/day. **Tables 3** and **4** show the results of univariable regression analysis evaluating the relationship between CCIMT and all interesting variables.

Table 1. Demographic and clinical characteristics of the 29 participants with systemic lupus erythematosus

Characteristics	Mean ± SD or Number (%)	Range
Female sex	24 (83)	
Age at enrollment (y)	25.1 ± 3.8	18.3–31.9
Age at diagnosis of SLE (y)	13.8 ± 2.6	8–17.7
Duration of SLE (y)	11.3 ± 4.2	3.7–19.4
History of renal involvement	26 (89.6)	
Metabolic equivalent of task	1.19 ± 0.93	0.1–3.9
Body mass index (kg/m^2)	22.4 ± 3.9	15.5–30.5
Proteinuria, persistent, n = 28	8 (28.6)	
Impaired renal function	4 (13.8)	
CCIMT (μm)	690 ± 150	470–966

CCIMT = common carotid intima-media thickness, SD = standard deviation, SLE = systemic lupus erythematosus

Table 2. Difference in common carotid intima-media thickness according to classic risk factors for atherosclerosis

Risk factors	Number	CCIMT (μm)*	*P*†
Sedentary lifestyle			
Yes	27	665 (470, 966)	0.08
No	2	529 (526, 533)	
Dyslipidemia			
Yes	20	728 (471, 966)	0.15
No	9	598 (470, 871)	
Overweight			
Yes	11	796 (538, 966)	0.08
No	18	616 (470, 890)	
Hypertension			
Yes	9	796 (471, 966)	0.28
No	20	636 (470, 890)	
Insulin resistance (n = 26)			
Yes	3	635 (585, 796)	0.93
No	23	663 (470, 966)	
Premature coronary heart disease in family			
Yes	3	555 (470, 803)	0.31
No	26	664 (471, 966)	

*median (min, max), † Mann–Whitney *U* test

Table 3. Relationship between common carotid intima-media thickness and continuous variables evaluated by univariable regression

Variables	B (95% CI)	*P*
Demographic features		
Age at enrollment	19.1 (5.3, 32.8)	0.008
Age at diagnosis of SLE	19.7 (5.6, 21.9)	0.08
Duration of SLE	8.1 (–5.6, 21.9)	0.23
Body mass index	12.7 (–1.7, 27.0)	0.08
Metabolic equivalent of task	–57.4 (–117.1, 2.3)	0.06
Laboratory test		
Hemoglobin	–34.7 (–71.3, 2.0)	0.06
White blood cells	–0.004 (–0.03, 0.02)	0.72
Lymphocyte	0.005 (–0.06, 0.07)	0.89
Platelets	0 (–0.001, 0.000)	0.31
Serum creatinine	117.2 (–142.1, 376.6)	0.36
Plasma glucose	4.0 (–3.7, 11.7)	0.30
Insulin	–0.49 (–8.7, 7.7)	0.9
Cholesterol	0.67 (–0.7, 2.0)	0.33
Triglyceride	0.27 (–0.3, 0.9)	0.35
Low density lipoprotein	0.55 (–1.2, 2.3)	0.52
High density lipoprotein	1.18 (–2.9, 5.3)	0.56
High-sensitivity C-reactive protein	5.13 (–41.3, 51.5)	0.82
Erythrocyte sedimentation rate	1.6 (–1.2, 4.4)	0.25
Anti-double-stranded DNA	0.2 (–0.05, 0.4)	0.11
C_3	–1.3 (–3.5, 0.9)	0.22
Medication		
Prednisolone, average dose	0.02 (–9.9, 9.9	0.99
Cyclophosphamide, cumulative dose	0.02 (–0.02, 0.06)	0.23
Azathioprine, cumulative dose	0 (–0.003, 0.001)	0.51

CI, confidence interval, SLE = systemic lupus erythematosus

Table 4. Relationship between CCIMT and categorical variables evaluated by univariable regression

Variables	B (95% CI)	*P*
Demographic features		
Female sex	56.2 (–96.3, 208.8)	0.46
Renal involvement	100.4 (–86.6, 287.5)	0.28
Overweight	104.3 (–8.4, 217.0)	0.07
Insulin resistance	–23.1(–218.4, 172.2)	0.81
Hypertension	83.3 (–38.2, 204.8)	0.17
Dyslipidemia	91.5 (–29.1, 212.1)	0.13
Impaired renal function	132.6 (–27.9, 293.2)	0.10
Premature coronary heart in family	–90.2 (–278.1, 97.7)	0.33
Sedentary lifestyle	172.6 (–46.9, 392.0)	0.12
Laboratory variables		
Leukopenia	–20.5 (–156.4, 115.3)	0.76
Lymphopenia	–86.2 (–197.7, 25.2)	0.12
Lupus anticoagulant, positive	2.53 (–127.8, 132.8)	0.97
Anti-cardiolipin, positive	–88.7 (–315.8, 138.5)	0.43
Persistent proteinuria	156.9 (42.3, 271.6)	0.009
Medication		
Cyclosporin use	255.7 (49.3, 462.2)	0.02
Tacrolimus use	114.7 (49.3, 462.2)	0.31

CCIMT = common carotid intima-media thickness

The analysis suggested the following variables to be significantly associated with increased CIMT: increasing age, persistent proteinuria, and cyclosporin use. The variables with $P < 0.1$, including age at enrollment, age at diagnosis of SLE, overweight, MET, hemoglobin, persistent proteinuria and cyclosporin use, were re-evaluated in multivariable regression. Similarly, the final model of analysis showed a significant relationship between CCIMT and each of the above variables including increasing age, persistent proteinuria and cyclosporin use with $P = 0.023$, 0.017, and 0.025, respectively (**Table 5**).

Table 5. Relationship between CCIMT and categorical variables evaluated by multivariable regression

	B (95% CI)	*P*
1st model		
Age at enrollment	11.4 (–1.7, 24.5)	0.09
Age at diagnosis of SLE	7.4 (–12.4, 27.2)	0.44
Overweight	59.5 (–40.9, 159.9)	0.23
Metabolic equivalent of task	–10.7 (–69.3, 47.9)	0.71
Hemoglobin	–14.1 (–49.0, 20.9)	0.41
Persistent proteinuria	89.0 (–23.2, 201.3)	0.11
Cyclosporin use	153.4 (–37.4, 344.3)	0.11
Final model		
Age at enrollment	14.1 (2.1, 26.1)	0.02
Persistent proteinuria	122.9 (24.1, 221.7)	0.02
Cyclosporin use	198.7 (26.7, 370.8)	0.03

CCIMT = common carotid intima-media thickness, SLE = systemic lupus erythematosus

Discussion

The classic risk factors such as being overweight, dyslipidemia, hypertension, and metabolic syndrome are common in the patients with SLE [16-18]. These factors, together with the consequences of SLE and its treatment, put the patients at higher risk of atherosclerosis. The early lesions of atherosclerosis most often arise from accumulation of lipoproteins within the arterial wall causing inflammatory responses, leukocyte recruitment, smooth muscle cell proliferation, and increased extracellular matrix. The ongoing inflammation, apoptosis, and fibrous changes lead to more advanced lesions, such as atherosclerotic plaques and calcification [19].

CCIMT has been considered to be a surrogate marker of CVD and a reliable measure of early atherosclerosis [20]. Although there are some previous studies demonstrating an increase in CCIMT in juvenile-onset SLE, most enrolled participants in these studies were adolescents [7-9, 21, 22]. We only recruited young Thai adults who developed SLE during childhood in the present study. Mean CCIMT of all measurements in each participant was used for our analysis. When compared with the previous studies in juvenile-onset SLE, we found greater CCIMT in participants. However, CCIMT usually progresses with increasing age as a rate of 0.005 mm/year in healthy adults reported by the Reference Values for Arterial Measurements Collaboration [23], and at an even faster rate in the adults with SLE [24]. Because of the lack of normal age-matched control group in our study, we could not absolutely conclude that there is an abnormal increase in CCIMT in our participants. Therefore, the CCIMT of our participants was further analyzed by comparing with CCIMT (μm) estimated by the sex-specific equations for percentiles of CCIMT across age in a healthy population ($321.7 + 4.971 \times$ age, for women; $323.5 + 5.201 \times$ age, for men [23]) according to the age of our participants. We found the mean CCIMT (SD) of the age-matched healthy population was 447 (76) μm, which was significantly less than the thickness found in our participants (690 (150) μm, $P < 0.001$).

Albuminuria has been regarded as an indicator of endothelial abnormalities at a renal level. It is usually associated with signs of cardiovascular damage in hypertensive or diabetic patients [25]. The associations between albuminuria and subclinical atherosclerosis was also reported in human immunodeficiency virus-seropositive adults by Tongma et al. [26]. In the Shanghai Changfeng Study, Ma et al. [27] reported that microalbuminuria was independently associated with carotid atherosclerosis in middle-aged people who had neither hypertension nor diabetes. Yang et al. [28] retrospectively studied 139 patients with SLE and found proteinuria was an independent risk factors for CVD compared with age and gender-matched controls. Concordantly, in young Thai adults with juvenile-onset SLE, our results demonstrated a relationship between persistent proteinuria and CCIMT. Although almost all of our participants had a history of renal involvement, several inflammation pathways in SLE are involved in the pathogenesis of atherosclerosis [6, 29] and could be responsible for renal endothelial injury leading to persistent proteinuria. Schanberg et al. [21] reported increased CIMT in patients with SLE who received low-dose prednisone. By contrast, there was decreased CIMT in patients given a moderate dose. Presence of ongoing active inflammatory disease because of inadequate immunosuppression may also be involved in atherosclerotic changes in SLE.

Calcineurin inhibitors cyclosporin and tacrolimus, the mainstay of immunosuppressive therapy in solid organ transplantation, has been used in combination with corticosteroids for patients with lupus nephritis who do not tolerate or respond to standard treatments [30]. Cyclosporin might be associated with increased susceptibility to atherosclerosis because of dyslipidemia, which may be related to abnormal low-density lipoprotein metabolism, or to altered bile acid synthesis and secretion [31]. We found that cyclosporin use in SLE might predict atherosclerotic change in the patient. Two participants who used cyclosporin had dyslipidemia and hypertension. However, the multivariable analysis results, based on only few participants receiving cyclosporin, might mislead interpretation. Sazliyana et al. [32] studied 82 SLE patients mean age of 34 years and showed that a cumulative dose of cyclosporin was negatively correlated with CCIMT. Oryoji et al. [33] studied 94 SLE patients with mean age of 44 years and suggested that use of cyclosporin in SLE could prevent atherosclerosis. This raises the possibility that cyclosporin could have antiatherosclerotic effects via its anti-inflammatory action; inhibiting proliferation and migration of endothelial cells, smooth muscle cells, and macrophages [31]; all of which are important in the pathogenesis of atherosclerosis.

Conclusion

Young adults with juvenile-onset SLE can develop earlier onset of subclinical atherosclerosis identified by abnormal CCIMT. Increasing age, persistent proteinuria and use of cyclosporin might hasten atherosclerosis in these patients. Our findings suggest that regular screening for subclinical atherosclerosis at young age is necessary for the patients with juvenile-onset SLE, particularly those with prognostic or other risk factors for atherosclerosis.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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