Atherosclerosis prevalence and the correlation between atherosclerosis risk factors and carotid intima-media thickness in below 40-year-old women with systemic lupus erythematosus

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ABSTRACT
Objectives: To determine the prevalence of atherosclerosis in female systemic lupus erythematosus (SLE) patients aged below 40 years old and the factors correlated with carotid intima-media (CIM) thickening.
Methods: A cross-sectional study was conducted on 80 female SLE respondents aged below 40 years old who were either in- or outpatient of Cipto Mangunkusumo General Hospital, Jakarta. History of disease and treatment was taken, and laboratory test and ultrasonography of the carotid artery to evaluate CIM thickness were performed.
Results: The prevalence of atherosclerosis was 40%, comprising of CIM thickening and/or presence of atherosclerotic plaque in the carotid artery. The median values of CIM thickness in the right common carotid artery, right carotid bulb, left common carotid artery, and left carotid bulb were 0.040 cm, 0.04535 cm, 0.0430 cm, and 0.047 cm, respectively. There was also a positive correlation reported of CIM thickness with increased age, the duration of SLE disease, and the duration of steroid treatment.
Conclusions: We found a positive correlation of CIM thickness with age, the duration of SLE disease, and the duration of steroid treatment in female SLE patients aged below 40 years.

Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad clinical manifestation including that of the coronary artery (10%).[1–7] Female SLE patients have 50 times the risk of suffering a myocardial infarction with a death rate varying between 6 to 16%.[4,6–8] The mechanism of premature atherosclerosis is as follows: arterial inflammation, arterial intima and media layer degeneration, immune response as a reaction to the immune complex, fibroblast and smooth muscle proliferation, and the presence of prothrombic condition.[4,9–16] Setiawan reported that endothelial dysfunction was present in 10% of SLE patients that underwent flow-mediated dilatation.[17]

The risk factors for acquiring premature atherosclerosis in SLE patients are: old age, long duration of disease, high disease activity, kidney involvement, steroid treatment, hypercholesterolemia, absence of immunosuppressive therapy, and hydroxychloroquine.[4,7,11–13,16–24] Bulkey and Robert reported that steroid administration of more than 1 year was associated with stenosis of the coronary artery lumen in 42% of SLE patient.[25] In addition, Petri et al also reported a decrease in serum cholesterol level by 8.9 mg% after administration of 200 mg or 400 mg of hydroxycholoroquine.[26]

Ultrasonography (USG) of the carotid artery is recommended by the American Heart Association as a diagnostic tool for subclinical atherosclerosis.[7,23,27] Roman et al reported that the prevalence of atherosclerotic plaque was 37.1%.[28] Doria et al found carotid intima-media (CIM) thickening in 28% of patients and atherosclerotic plaque in 17% of patients.[29] Sato et al reported that atherosclerotic plaque was found only in SLE patient group (36%).[30] Selzer et al reported that 32% of SLE patients had a minimum of one focal atherosclerotic plaque.[31] The same result was also reported by Manzi et al in which 40% of SLE women had atherosclerotic plaque.[32] However, Jimenez et al did not find any differences in CIM thickness between the SLE patient group and the control group.[33] Besides traditional factors, the SLE disease itself is a risk factor for atherosclerosis.[4,11,13,20,21,34–46] Carotid artery USG was used to evaluate the diameter of the artery, thickness of CIM, presence of plaque and its extent.[22,47,48] Increased CIM thickness is associated with increased risk of cardiovascular incidence.[7,49–57] Ziembicka et al, who conducted a study on 558 respondents with a mean age of 58.8 years, reported that there was a significant correlation between CIM thickness and the severity of the coronary artery disease that was evaluated using coronary angiography (p<0.00001).[58]

The objective of this study was to determine the prevalence of atherosclerosis in female SLE patients below 40 years old to find the role of SLE disease in the prevalence of atherosclerosis and also to find the correlation between risk factors for atherosclerosis and CIM thickness evaluated using carotid artery USG.

METHODS

The study was conducted in the Department of Internal Medicine, Cipto Mangunkusumo General Hospital, Jakarta from November 2008 until April 2009 using a cross-sectional study design. The samples were female SLE outpatients and inpatients with a maximum age of 40 years who fulfilled the 1997 update of 1982 American College of Rheumatology revised criteria. The exclusion criteria are patients with a neck mass or neck ulcer and patients that could not be examined in supine position.

Variables measured

Risk factor for atherosclerosis

Interviews were done to find the characteristics of samples that included age, duration of disease, presence of hypertension or diabetes mellitus, type and duration of treatment given (steroid, chloroquine, immunosuppressants). Measurement of blood pressure and body mass index were performed. Assessment of disease activity was conducted once using the Mexican SLE Disease Activity Index (Mex-SLEDAI) scoring system. Laboratory tests were done to assess the disease activity, determine the random blood glucose level, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and blood triglyceride. Random urine test and 24-hour quantitative urine protein test were also conducted to detect any kidney disorder.

Carotid artery ultrasonography examination

The measurement of CIM thickness was performed using Philips Sonos 5500 B-mode ultrasound by a certified operator. In patients with supine position, examination of CIM thickness was performed on the following locations: left/right mid-common carotid artery (LCCA/RCCA) and left/right carotid bulb and each from the following angles: anterior, lateral, and posterior. The results of the examination of CIM thickness were reported in centimeters and derived from the mean CIM thickness of 3 locations examined (anterior, lateral, and posterior).

The normal value of the common carotid artery intima-media (IM) thickness is determined based on the following equation:

$$\text{IM thickness of the common carotid artery} = 0.04 \text{ cm} + \{(\text{age} - 21) \times 0.001 \text{ cm}\}$$

The above equation is determined based on the results of previous studies conducted by Maarifat who reported that the mean CIM thickness of the normal population at the mean age of 21 years was 0.04 cm and the normal growth of the common carotid artery in women was 0.001 cm a year.[56,57] For normal IM thickness of the carotid bulb, the reference value used was 0.83 cm which is the maximum thickness of IM of the carotid bulb in the normal group at ages 35-39 years according to a study conducted by Lim and Kooner.[53]

Atherosclerosis was reported if there was CIM thickening in at least one location: left/right mid-common carotid artery or left/right carotid bulb and/or the presence of atherosclerotic plaque in one or more of the above locations. Atherosclerotic plaque was defined if the CIM thickness was >0.13 cm in at least one location.

Statistical methods

Data processing was conducted using Statistical Package for the Social Sciences (SPSS) version 17.00. Bivariate analysis was conducted between risk factors for atherosclerosis and CIM thickness using the Pearson's correlation test or its alternative (Spearman's test).

RESULTS

Of the 80 respondents studied, the mean age was 26.93 years (table 1) with an educational level of mostly high school degree or its equivalent.

Table 1 Distribution of variables contributing to atherosclerosis

Age, years, mean (SD)	26.93 (6.342)
Duration of disease, months*	31 (0.07–222)
Duration on steroid, months*	19 (0.03–222)
Daily steroid dose, mg*	15 (1.25–625)
Body mass index, kg/m²*	21.35 (12.89–44.40)
Mex-SLEDAI score*	3 (0–24)
Random blood glucose, mg/dL*	88 (66–187)
Total cholesterol, mg/dL*	180.5 (60–383)
LDL cholesterol, mg/dL, mean (SD)	113.45 (39.59)
HDL cholesterol, mg/dL, mean (SD)	58.71 (22.19)
Triglyceride, mg/dL*	121 (43–636)

*Data have abnormal distribution; values are median (range).
Mex-SLEDAI, Mexican Systemic Lupus Erythematosus Disease Activity Index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

In the distribution of risk factors for atherosclerosis, absence of chloroquine treatment (87%), daily steroid dose of more than 10 mg (60%), and active SLE disease (60%) ranked the highest in the list (table 2).

Table 2 Distribution of characteristics based on risk factors for atherosclerosis

Characteristics	n (%)
Absence of chloroquine (3 months minimum)	70 (87.5)
Active SLE (Mex-SLEDAI score ≥ 2)	48 (60)
Daily dose of steroid (prednisone) >10 mg/day	48 (60)
Long-term steroid treatment (>12 months)	46 (57.5)
Kidney involvement	45 (56.2)
Hypertriglyceridemia	32 (40)
Hypercholesterolemia	27 (33.8)
Hypertension	22 (27.5)
Duration of disease >5 years	13 (16.3)
Obesity	13 (16.3)
Diabetes mellitus	0 (0)
Smoker	0 (0)

SLE, systemic lupus erythematosus; Mex-SLEDAI, Mexican SLE Disease Activity Index.

From the assessment of SLE activity using the Mex-SLEDAI score, the disorder mostly found was kidney disorder (36.3%), followed by lymphopenia (30%), mucocutaneous disorder (18.8%), complaints of unexplained fatigue (17.5%),

and hematological disorder such as hemolysis (15%), leukopenia (10%), and thrombocytopenia (7.5%).

The prevalence of atherosclerosis was 40%, as seen in more detail in table 3.

Table 3 Prevalence of atherosclerosis in female systemic lupus erythematosus patients

Criteria	n	(%)
CIM thickening without carotid plaque	28	(35)
CIM thickening with carotid plaque	3	(3.8)
Carotid plaque without CIM thickening	1	(1.2)
Atherosclerosis	32	(40)

CIM, carotid intima-media.

The distribution of CIM thickness in all respondents can be seen in table 4.

Table 4 Carotid intima-media (CIM) thickness evaluated using B-mode ultrasound

Characteristics	Median (range)
RCCA IM thickness, cm	0.0400 (0.030–0.070)
Right carotid bulb IM thickness, cm	0.0435 (0.030–0.183)
LCCA IM thickness, cm	0.0430 (0.030–0.073)
Left carotid bulb IM thickness, cm	0.0470 (0.030–0.090)

All data have abnormal distribution.
RCCA, right mid-common carotid artery; IM, intima-media; LCCA, left mid-common carotid artery.

The Pearson's correlation test or its alternative (Spearman's test) that was performed between the risk factors for atherosclerosis and CIM thickness showed a positive correlation between age and CIM thickness in RCCA, LCCA, right and left carotid bulb, and also a positive correlation between the duration of SLE disease and CIM thickness in LCCA. In addition, there was a positive correlation between the duration of steroid treatment and CIM thickness in RCCA, right carotid bulb, and LCCA.

Pearson's correlation test showed no significant correlation of total cholesterol level, LDL cholesterol level, systolic blood pressure, duration of chloroquine treatment, proteinuria level, or score of disease activity with CIM thickness of SLE patients.

DISCUSSION

This study was focused on below 40-year-old SLE patients. As we know, older age is one of the risk factors for premature atherosclerosis in SLE patient. Some previous studies also reported high prevalence of atherosclerosis in above 40-year-old SLE patients. In those patients, we could not assess whether the atherosclerosis was influenced predominantly by older age or by the disease itself. In this study, we wanted to learn more about SLE as the main risk factor for premature atherosclerosis; therefore, we chose SLE patients below 40 years old as respondents.

Prevalence of premature atherosclerosis in SLE patients is influenced by traditional risk factors and risk factors associated with the SLE disease itself. The study showed the distribution of prevalence of hypertension was 27.5%, obesity was 16.3%, hypercholesterolemia was 33.8%, and hypertriglyceridemia was 40%. As the respondents' mean age of 26.93 years old was a relatively young age, it was more likely that the prevalence of hypertension, obesity, and dyslipidemia that occurred was associated with the effects of treatment or the SLE disease itself rather than purely associated with the traditional risk factors. Jimenez and Manzi reported that SLE patients who had hypertension, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, and elevated apolipoprotein B level had a higher risk of developing atherosclerosis.[33] However, Svenungson reported that there was no significant correlation between blood pressure, body mass index score, and diabetes mellitus of SLE patients with a history of cardiovascular disease and of SLE patients without a history of cardiovascular disease or those of the control group.[38]

This study found that more than half of the respondents were aged between 21 and 30 years old with a mean of 26.93 ± 6.342 years. The mean age of SLE patients found in this study was the youngest mean age compared to the studies done in other countries. This is interesting because sunlight, which is found more abundant in Indonesia as a tropical country, may be one of the triggers for an earlier onset of SLE so that the mean age of SLE patients in Indonesia was younger than in the four-seasonal countries.

For the duration of disease variable, the median was 31 months. Compared to previous studies, the median of duration of disease was the shortest although it is reported that the

Tabel 5 Pearson's correlation coefficients between atherosclerosis risk factors and carotid intima-media (CIM) thickness

Risk factors	CIM thickness			
	RCCA	Right bulb	LCCA	Left bulb
Age	0.227 (0.021)	0.289 (0.004)	0.389 (0.0001)	0.387 (0.0001)
Duration of SLE disease	0.182 (0.053)	0.182 (0.053)	0.189 (0.047)	0.070 (0.268)
Total cholesterol level	−0.028 (0.399)	−0.065 (0.283)	0.080 (0.239)	−0.014 (0.450)
LDL cholesterol level	−0.048 (0.335)	−0.107 (0.177)	0.100 (0.189)	0.037 (0.372)
Systolic blood pressure	0.045 (0.347)	0.045 (0.346)	0.060 (0.298)	0.110 (0.166)
Duration of steroid treatment	0.195 (0.041)	0.202 (0.036)	0.238 (0.017)	0.124 (0.135)
Duration of chloroquine treatment	−0.284 (0.134)	0.007 (0.489)	−0.159 (0.271)	0.0004 (0.499)
Proteinuria level	−0.056 (0.311)	−0.069 (0.273)	0.062 (0.291)	−0.035 (0.380)
Mex-SLEDAI score	−0.014 (0.449)	0.040 (0.360)	−0.117 (0.151)	0.054 (0.316)

Data are given as r (p value). RCCA, right mid-common carotid artery; LCCA, left mid-common carotid artery; SLE, systemic lupus erythematosus; LDL, low-density lipoprotein; Mex-SLEDAI, Mexican SLE Disease Activity Index.

maximum duration of disease was 222 months. The low value of duration of disease shows that the survival rate was still low in the SLE patients of this study.

All the respondents in this study were given steroid as a main treatment. As many as 57.7% respondents were given steroid treatment for more than 12 months with a median duration of steroid treatment of 19 months and a median daily dose of steroid of 15 mg/day (equivalent to prednisone). A steroid daily dose of more than 10 mg/day and a steroid treatment of more than one year were reported as risk factors that accelerate the onset of atherosclerosis in SLE patients. Bulkey and Robert in 1975 conducted an autopsy to examine the hearts of 36 SLE patients who were given steroid treatment of more than one year and reported that 42% of patients had stenosis of more than 50% of the lumen of the coronary artery.[25] MacGregor and Petri also reported that a daily dose of prednisone of more than 10 mg/day in SLE patients could increase the incidence of dyslipidemia (hypertriglyceridemia, hypercholesterolemia).[6,21,42]

It is apparent that steroid was the first choice of treatment in this study although it is known that long term steroid treatment has side effects that includes diabetes mellitus, hypertension, dyslipidemia that is also a risk factor for atherosclerosis. This steroid treatment is like a double edged knife—if the dose is more than 10 mg/day, it will increase the incidence of dyslipidemia that is associated with the incidence of atherosclerosis risk, but Roman also reported that the incidence of atherosclerotic plaque is associated with low dose of steroid. It means the SLE disease was not yet well controlled in those cases.

Chloroquine treatment for at least three months is considered to have a protective effect against atherosclerosis through its hypolipidemic effect; however, in this study only 12.5% respondents were treated accordingly. Hydroxychloroquine, which has a positive effect in treatment of skin and joint disorders, is also reported to be able to decrease the total cholesterol, LDL cholesterol, and triglyceride level so that it could reduce the risk of atherosclerosis.[13,26,43] Wallace et al found that lower levels of cholesterol, triglyceride, and LDL-C cholesterol were significant in female SLE patient group that were given hydroxychloroquine treatment without steroid administration.[43] The low frequency use of chloroquine was caused by its use in SLE that was limited for only musculoskeletal involvement, while according to the description of organ disorders in the Mex-SLEDAI score in this study, mucocutaneous involvement was 18.8% and arthritis involvement was 3.8%.

The assessment for disease activity using Mex-SLEDAI score showed that 60% of the respondents were in the active form of the disease with a median score of 3. The high score of disease activity was likely caused by the SLE condition that was actually still active during initial treatment or there was a period of fluctuating disease activity because the respondents did not undergo the treatment program regularly. This was possibly associated with the low awareness and low income levels of the respondents. The low income level was reflected in the occupational status of the respondents. Only 27.5% of the respondents held a job and 78.7% got treatment using the welfare facility.

The USG examination of the carotid had 93.4% sensitivity and 94% specificity to evaluate the process of atherosclerosis. The features found on the carotid arterial wall is a reflection of the features found on the coronary arterial wall. A thickening of CIM that precedes plaque formation or discovery of plaque in carotid artery could be used as a window to evaluate the process of atherosclerosis in coronary artery.[7,23,27] Images of USG can visualize the arterial wall in each stage of atherosclerosis from the normal stage to total arterial occlusion stage. The measurement of IM of carotid artery could be used as a marker of the development of atheroma and is associated with the incidence of coronary heart disease, stroke, and peripheral arterial disease.[27]

As this study was conducted on respondents with a young mean age, it is hoped that measurement of CIM thickness gives a clearer picture of the carotid artery condition caused by the effect of SLE disease itself or by the side effect of treatment. Other factors such as hypercholesterolemia, hypertriglyceridemia, and obesity are considered as caused by the SLE disease or the side effects of steroid treatment rather than as comorbids.

Table 6 Studies on the prevalence of atherosclerosis in systemic lupus erythematosus (SLE) patients

Researchers	Study design and results
Manzi, USA, 1999[32]	A cross-sectional study of 175 female SLE patients found that the prevalence rate of atherosclerosis was 40% and the mean age was 50.5 ± 11.7 years.
Roman et al, New York, 2003[28]	A case-control study of 394 SLE patients found that the prevalence rate of atherosclerotic plaque was 37.1% and the mean age was 52 years.
Doria et al, Italy, 2003[29]	A prospective cohort study of 78 SLE patients found that the prevalence rate of atherosclerotic plaque was 17% and the mean age was 45.7 years. There was also carotid intima-media (CIM) thickening in 28% of the patients with a mean age of 43.3 years.
Selzer et al, USA, 2004[31]	A cross-sectional study of 214 female SLE patients without cardiovascular disease found that the prevalence rate of atherosclerotic plaque was 32% and the mean age was 52.6 ± 9.7 years.
Sato et al, Japan, 2007[30]	A case-control study of 78 female SLE patients who were clinically stable for at least 3 years with a fixed dose of prednisone of more than one year found that the prevalence rate of atherosclerotic plaque was 36% and the mean age was 42.3 years (premenopause) and 56.8 years (postmenopause).
This study	A cross-sectional study of 80 SLE patients with a maximum age of 40 years old found that the prevalence rate of atherosclerosis (with thickening of CIM and/or atherosclerotic plaque) was 40% and the median age was 24.8 years old.

The high prevalence rate of atherosclerosis in this study was caused by the differences in normal CIM thickness reference values of healthy respondents used. The previous study used the same reference value of normal CIM thickness for all age groups. This study used a reference value of normal common carotid intima-media (CCIM) thickness that was calculated based on an equation determined by the researcher.

Based on the study conducted by Maarifat in 2005, the mean value of the CCIM thickness in the Indonesian healthy subjects aged 21 years was 0.04 cm and the Atherosclerosis Risk in Communities (ARIC) study by Howard in 1993 found the normal growth of the common carotid arterial wall was 0.001 cm/year in healthy female respondents. Therefore, the equation for normal CCIM thickness could be determined. By using the reference value of normal CIM thickness based on age, we can determine any increase of CCIM thickness in each stage of age so that we can anticipate the steps for further treatment to prevent atherosclerosis.

In the Pearson's correlation test or its alternative (Spearman's test) between the risk factor for atherosclerosis and CIM thickness, we found a positive correlation between increased age, longer duration of SLE disease, and/or longer duration of steroid treatment and CIM thickness.

Aging and duration of SLE disease were reported to have a positive correlation with CIM thickness. A previous study conducted by Selzer and Manzi found that old age is associated with increased risk of CIM thickening and development of atherosclerotic plaque.[31,32] Manzi et al and other studies also reported a significant correlation between the duration of SLE disease and the prevalence of atherosclerotic plaque.[32] Swaak et al also reported the prevalence of myocardial infarction (5%) and coronary artery disease (8%) in patients that have suffered SLE for ten years.[5]

There was also a report of a positive correlation between long duration of steroid treatment and CIM thickness. This is in line with the theory that steroid is one of the risk factors for atherosclerosis that is formed because of the effects of dyslipidemia, hypertension, diabetes mellitus, and obesity. Manzi et al also reported that female SLE patients administered with a longer duration and a higher cumulative dose of prednisone had a higher risk of developing atherosclerotic plaque.[32] In addition, Bulkey also reported the presence of more than 50% stenosis in the coronary artery lumen in SLE patients who had undergone steroid treatment continuously for more than one year.

Steroid, which is a drug of choice for SLE treatment, must be administered wisely because treatment with steroid has two effects: anti-inflammatory and atherogenic effect. In these cases, steroid must be administered appropriately in terms of dose and duration of treatment. Regular monitoring must be conducted to anticipate the possibilities of side effects that occur.

We understand that atherosclerosis develop as a result of various factors including inflammation factor that is characterized by an imbalance between proinflammatory cytokine and anti-inflammatory cytokine. Because of limited funds and examination methods, an examination of inflammation marker could not be performed in this study. In addition, the cross-sectional study design used here did not allow the researcher in this study to directly evaluate the cause and effect association between the risk factors and the prevalence of atherosclerosis.

The limited reference value of normal CIM thickness in the Indonesian population that is limited to a certain age group as reported by Maarifat in 2005 forced the researcher to create an equation to determine the normal thickness value of the common carotid intima-media.

CONCLUSIONS

Atherosclerosis occurred in 40% young aged female SLE patients as CIM thickening and/or carotid plaque. There was positive correlation of CIM thickness with age, duration of SLE disease, and duration of steroid treatment in female SLE patients aged below 40 years.

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