The effect of disease duration on the incidence of peripheral arterial disease in young adults with systemic lupus erythematosus

M Merlyn, B Setyohadi, S Soebardi, K Harimurti

Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta

ABSTRACT

Background: Peripheral arterial disease is a chronic complication that affects morbidity and mortality in SLE patient. However, there were only a few of researches studying the relationship of disease duration and peripheral arterial disease event overseas and it has never been studied in Indonesia.

Objectives: To obtain information about the increased event of peripheral arterial disease in women of 40 years old or younger with SLE's duration of five years or longer compared with less than five years.

Methods: This was a case control study conducted between June - August 2012 at Cipto Mangunkusumo hospital, Jakarta. Subjects were women of 40 years old or younger with SLE who visited Rheumatolgy and Allergy-Immunlogy outpatient clinic. They were assigned to case and control groups and traced retrospectively using interview and medical record. The relationship between disease duration and peripheral arterial disease was estimated using OR and the role of confounding factors was analysed using logistic regression one by one, resulted in fully adjusted OR.

Results: A total of 90 subjects were recruited, 18 subjects in case group and 72 subjects in control group. Traditional risk factors were similiar in both groups. In multivariat analysis, there was a relationship between disease duration 5 years or longer and peripheral arterial disease with fully adjusted OR 1,9 (95%CI 0,575-6,543). Older age and steroid therapy were the confounding factors.

Conclusion: There was an increased event of peripheral arterial disease in women of 40 years old or younger with SLE's duration five years or longer compared with subjects having the disease duration less than five years, but this increase was not statistically significant.

Keywords: Peripheral arterial disease, lupus erythematosus systemic, disease duration

---

The fast development of medical technology affects the life expectancy of people with SLE.[1] But this increase of life expectancy brings new challenges as the patients will have complications associated with the accumulation of chronic damage on organs. Without early detection and promp treatment, there will be decreased quality of life with increased morbidity and mortality. One of these potential chronic damages is vascular damage caused by early atherosclerosis. According Urowitz et al (1976), the distribution of death causes in SLE was bimodal where the early death was caused by the disease severity or infection, while the late cause was cardiovascular reasons.[2] Young women with SLE have five times more risk for a cardiovascular event compared with normal control on the same age. This risk increases with age, disease duration, hypertension, dyslipidemia, body mass index, and CRP.[3,4] In a cohort study on 78 SLE patients without atherosclerosis signs, after five years there were increased thickness on 28% patients and atherosclerotic plaque on 17% patients.[5] Traditional risk factors could not explain the early pathogenesis of atherosclerosis in SLE, so it was postulated that autoimmune processes causing chronic inflammation was the main contributor. [6,7] Vascular complications in SLE should have enough attention because the process happens even before symptoms could appear.[8] Peripheral arterial disease (PAD) is one example of these vascular complications. PAD usually asymptomatic and does not have classical symptoms that it hinders early diagnosis.[9] It became the cause of decreased quality of life in more than two millions of patients in USA, which affected morbidity, mortality, and increased health spending.[10] SLE patients (mean age 39 years old) were reported having prevalence of abnormal ankle-brachial index (ABI) higher than normal population (37% vs 4%)[11] The effect of disease duration on the increasing event of PAD in SLE patients have not been studied enough. A few of studies overseas such as Burgos et al (LUMINA, 2009) [12] in USA, Bhatt et al (2007)[13] in India, and Wang et al (1993)[14] in China did not give adequate explanation on the relationship between the duration of SLE and this complication. In Indonesia, Sari RM (2009) did a study measuring the thickness of medial intima in the carotid artery of women younger than 40 years old with SLE. The study reported the prevalence of atherosclerosis about 40%, with duration of disease, age, and duration of steroid therapy were the factors with positive correlation.[15] Compared with USG, ABI was cheaper and easier for screening because of its good sensitivity and specificity.[16]

METHODS

Study design and subjects

This study was done in Rheumatology and Allergy-Immunology outpatient clinic in Cipto Mangunkusumo Hospital Jakarta between June-August 2012. The samples were taken consecutively and there were 104 subjects eligible for the study, which means they were SLE patients (diagnosis according to the revised ACR criteria in 1997) and younger than 40 years old. 14 subjects were excluded because 8 of them had mixed connective tissue disease, 5 refused to be included in the study, and the other was in her 26 weeks of pregnancy. After interview, medical record tracking, and physical examination, these 90 subjects had their ankle brachial index measured using ABI osilometry by one examiner in Endocrine and Metabolic outpatient clinic in Cipto Mangunkusumo Hospital. Subjects with ABI 0.9 or lower and more than 1.3 were put in the case group (peripheral arterial disease) and those with ABI of 0.9-1.3 were put in the control group.

All of the subjects were interviewed using the same questionnaire. The duration of disease was determined using the data from interview and medical records. Disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Any history of hypertension, DM, dyslipidemia, organs involvement, and therapy was taken from interview and medical records. Subjects with essential hypertension and DM before diagnosis of SLE were excluded.

Data analysis

Data analysis was done with SPSS ver. 16.0.0., using p-value less than 0.05 and CI of 95%. The relation of disease duration with PAD incidence was estimated in OR. Multivariat analysis were done using regression logistic resulted in fully adjusted OR, which was the value after analyzing the confounding factors.

RESULTS

Subjects characteristics

During the study period, there were 104 patients who came to Rheumatology and Allergy-Immunology outpatient clinic eligible for study subjects, but 14 patients were excluded leaving 90 subjects. 18 subjects were put into the case group and 72 subjects were put into the control group. The study was terminated before it had enough samples because there were not enough patients and limited time period. To expand the number of samples, the authors tried national registry of lupus patients, but a lot of the data were invalid.

Table 1 shows the characteristics of study subjects. The mean age was similar in both groups, which was 29.8 years old in the case group and 29 years old in the control group. Subjects in the case group had longer mean duration of disease than control group.

Table 1. Subjects characteristics

Characteristics	Case (n=18)	Control (n=72)	p Value
Mean age (years), SD	28.83 (8.20)	29 (6.62)	--
Duration of disease (months), SD	57 (3-178)	44.5 (1-260)	0.79
Mean BMI (SD)	22.1 (3.74)	21.5 (2.95)	--
Hypertension (%)	1 (5.6%)	3 (4.2%)	0.80
Diabetes Mellitus (%)	0	2 (2.7%)	0.48
Dyslipidemia	7 (38.9)	23 (31.39)	--
Kidney involvement	9 (50%)	28 (38.8%)	0.39
Mean disease activity score (SD)*	4.4 (3.05)	4 (3.68)	--
Chloroquine therapy	8 (44.4%)	20 (27.8%)	0.28
Steroid therapy	17 (94.4%)	71 (98.6%)	--
Mean duration of steroid therapy (months), SD	55.7 (41.17)	43 (45.21)	0.68

*disease activity score was assessed using Mex-Sledai, SD = Standard deviation,

Subjects in the case group had longer mean duration of disease than the control group. Both BMI and disease activity score in the two groups were similar. Traditional risk factors for atherosclerosis such as diabetes, hypertension, and dyslipidemia were also similar in both groups. There was no history of smoking and previous cardiovascular events in the groups. Kidney involvement happened more in the case group than control group. There were 2 subjects with diabetes mellitus in the control group, and it was because of steroid therapy. Chloroquin was more frequently used in case group while steroid was used by a lot of subjects in both groups.

The effect of disease duration on the incidence of peripheral arterial disease

Table 5.2 shows increased risk of PAD in subjects with duration of disease ≥5 but this increase is not significant statistically (*crude OR* 1,6 (CI 95% 0,559-4,576); p=0,38). This relation did not change after adding confounding factors such as chloroquine therapy, age, steroid therapy, proteinuria, disease activity score, dyslipidemia, and hypertension using logistic regression. The final result was fully adjusted OR 1.9 (CI 95% 0,575-6,543).

Table 2. Multivariate analysis of disease duration and its effect on PAD incidence after including confounding factors.

Variable	OR	CI 95%	P
Duration of disease			
Crude OR	1.6	0.559-4.576	0.38
Adjusted OR			
Chloroquine	1.5	0.511-4.348	0.46
Age	1.9	0.589-5.852	0.29
Steroid therapy	2.1	0.643-6.914	0.21
Proteinuria	1.9	0.595-6.557	0.26
Disease activity score	1.9	0.569-6.387	0.29
dyslipidemia	1.9	0.575-6.512	0.28
Hypertension (fully adjusted)	1.9	0.575-6.543	0.28

DISCUSSION

Demographic characteristics

In this study, the mean age on the case group was 28.83 years old (SD 8,2) and 29 years old on the control group (SD 6,62). The mean age in this study did not differ far from other studies such as Bhatt et al (2007) in India with mean age of 30.7 (SD 8,7).[13] But there were studies with older mean age, such as LUMINA (2009), a study with multiethnic samples in USA with mean age of 36,5 years old, while Liu et al (2009) in China reported mean age around 33,1 years old (SD 11,8).[12,17] Cardiovascular incidence in women without SLE were more common after 55 years old, but the same principle did not happen with the SLE group. Manzi et al did an epidemiologic study and reported that women with SLE between 35-44 years old had 5 times risk of cardiovascular incidence compared with the same age group without SLE.[3] Most of the subjects on both groups were jobless or housewives with moderate level of education (highschool). This affected their social economic status and their view about SLE. Most of the subjects had insurance so program such as routine examination, laboratory workups, and treatment choice depended on their insurance cover. Besides, a lot of patients lived outside Jakarta, or when they lived in Jakarta, they were far from the hospital. These affected their compliance for routine control or following treatment program.

Clinical characteristics

The subjects in case group tended to had longer duration of disease (57 months) compared with those in the control group (44.5 months). McDonald did a study in USA and Liu did too in China, they both reported longer duration of disease (112 months and 99 months). [12,17] But Bhatt in India reported shorter duration of disease with 49.4 months.[13] This variation was most probably caused difference in ethnicity and treatment. Traditional risk factors of atherosclerosis in both groups were similar. This finding was in accordance with previous studies. These traditional risk factors could not specifically explain the pathogenesis of early atherosclerosis in SLE and were not the primary causes.[18,19]

Subjects in the case group had more kidney involvement. Proteinuria is one of many factors causing early atherosclerosis in SLE, because it stimulates apolipoprotein and cholesterol synthesis in liver, resulting in hypercholesterolemia as a risk factor for atherosclerosis.[20]

Disease activity assessment using Mex-SLEDAI score showed both groups was in their active phase with mean value of 4.4 (SD 3.05) in the case group and mean value of 4 (SD 3.68) in the control group. This was similar with a study by Sari (2009) involving SLE women in Cipto Mangunkusumo Hospital as her subjects. Her study reported disease activity score of 3.[15.] High scores of disease activity were probably due to low compliance in treatment. This condition might be caused by low awareness affected by education level, economy level, and living places far from the hospital.

Most of the subjects in both groups had steroid as their main therapy, but one subject in each group did not have steroid. These subjects had mucocutaneous SLE and they were given chloroquine as main treatment. Those with steroid had it for long duration (more than 1 year), but mean duration of steroid therapy in control group was longer (55.7 months, SD 41.17) than in case group (43 months, SD 45.21). Long duration of steroid therapy was probably related to kidney involvement and high disease activity score.

The effect of disease duration on the incidence of PAD

Urowitz et al (1976) was the first to report that the late cause of death in SLE was secondary to cardiovascular disorder. The risk of cardiovascular incidence increased every year according to duration of SLE. Young women with SLE have five times more risk to experience cardiovascular incidence compared with their normal counterparts. This is caused by early atherosclerosis in SLE. Traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesitas, and sedentary life style have important roles in its formation, but a number of studies have proven that even after these risk factors were modified, those with SLE still have higher rate of cardiovascular incidence. Disease duration, high score of disease activity, kidney involvement, steroid therapy, chloroquine therapy, antiphospholipid antibody, and CRP are some factors related to the early atherosclerosis in SLE.[2] Analysis with logistic regression in this study showed clinically significant relation between the duration of disease with incidence of PAD (OR 1.9, CI 95% 0,559-4,576), but it was not significant statistically (p=0,37). This was caused by low number of samples, low power of study (<80%), and wide confidence interval. On the early estimation of samples, we assumed high OR (4), but in reality the OR estimated in the end was far below, and one of the reason the study was not clinically significant. After re-estimation, for power study of 80% the samples needed for both groups were 136 samples each. For the ratio of case : control 1:4, the study needed 85 in case group and 340 in control group.

OR value of 1.9 was clinically significant because the effect of PAD was significant in a patient's morbidity and mortality.four times more likely to die in ten years compared with patients without PAD.[21]

All subjects in case group were asymptomatic PAD with ABI <0.9. Low ABI (<0.9) in asymptomatic patients is related with morbidity and mortality. It also plays a role as biomarker in cardiovascular incidence. Asymptomatic PAD is related to decreased function of lower extremities in women older than 65 years old. [22] Asymptomatic PAD is also related to an

increase by 1.4 in total mortality and 1.5 increase of mortality with cardiovascular causes.[23] A systematic review involving 28,679 subjects reported consistent relationship between low ABI (<0.9) with prognosis of cardiovascular incidence. The specificity of low ABI (<0.9) in detecting coronary heart disease, stroke, and mortality caused by cardiovascular incidence were 92.7%, 92.2%, and 87.8% with positive likelihood ratio of 2.53, 2.45, and 5.61.[24]

The role of confounding variable in the relation between duration of disease and PAD incidence

In multivariate analysis using logistic regression, there were potential confounding variables consisted of age and duration of steroid therapy. These variables became the confounding variable because they changed OR value more than 10%, in which age changed adjusted OR for 24.5% and duration of steroid therapy changed adjusted OR for 13.5%. A few of studies reported the same result where age was a variable affecting PAD incidence in SLE.[12,17] Age can not be separated from disease duration, because longer disease duration means older age. Unlike patients without SLE, PAD in SLE happens early with increasing risk factors in accordance to the patient's increasing age.

The effect of steroid therapy on cardiovascular incidence in SLE is still controversial. Treatment using steroid is a dilemma. Inadequate treatment leaves room for inflammation as a trigger for early atherosclerosis, but long duration of steroid increases risk of dyslipidemia and hypertension as risk factors of atherosclerosis. Increased prednisone dose up to 10 mg/ day is related to the increase of cholesterol level by 7.5 mg/dl (SE 1.46) and increased mean arterial pressure by 1.1 mmHg.[25] McDonald et al reported duration of steroid therapy as a risk factor for PAD in SLE patients ($p<0.05$) in which case group received steroid for 109 months compared with control group (34 months). The mean daily dosage for case group was 14 mg/ day and 15 mg/ day for control group.[26] But Liu et al in their study about risk factors of digital gangrene in SLE patient stated that steroid did not have any role ($p=0.10$).[17] More than 5 years of steroid therapy is related with calsification on peripheral blood vessel and more severe clinical symptoms of PAD.[26] Because steroid effect is still controversial, confirming direct effect of steroid on PAD incidence needs further study.

Study limitation

One of limiting factors in this study was low number of samples, resulting in low power of the study (<80%). Low power made it difficult to gain statistically significant results. Other limiting factors were no measurement of inflammation factors and level of antibody anticardiolipin because of the limited fund and no reference on normal ABI of Indonesian.

Recall bias is a limitation in case control study, but in this study there were medical records to keep track of disease duration. With multivariate analysis, recall bias and confounding bias effects could be minimalized. Because there were no data about SLE population (study base), control group recruitment could not represent common population of SLE because they were taken from those coming to the hospital to get treatment, resulting in uncontrolled selection bias.

Study result generalization

In order to apply this study result to a wider population, the validity of this study needs to be assessed. Internal validity I of this study is good because there was no drop out subjects and all subjects had complete data about their risk factors. Internal validity II is not good enough because subjects in the control group were taken from patients who came to the hospital, causing selection bias and low representative power.

CONCLUSION

There was an increase of PAD incidence in SLE women aged ≤40 years old with SLE ≥5 years compared with <5 years, but it was not statistically significant.

REFERENCES

1. Gordon C. Long – term complication of systemic lupus erythematosus. Rheum. 2002;41:1095-1100
2. Urowitz MB, Bookman AAM, Koehler BE, Gordon DA, Smythe HA, Orgyzlo MA. The bimodal mortality pattern of SLE. Am J med. 1976;60:221-5
3. Manzi S, Selzer F, Tyrrell KS, Fitzgerald SG, Rairie JE, Tracy RP, dkk. Prevalence and risk factors of carotid plaque in woman with systemic lupus erythematosus and antiphopholipid syndrome. Rheum. 2005;44:756-61
4. Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, dkk. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circ. 2005;112:3337-45
5. Doria A, Schoenfeld Y, Wu R, Gambari P, Puato M, Ghiraraello A, dkk. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis. 2003;62(11):1071-7
6. Esdaile JM, Abrahamwicz M, Grodzizky T, Li Y, Panaritis C, Berger RD, dkk. Traditional Framingham risk factor fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2001;44:2331-7
7. Kaplan MJ. Premature vascular damage in systemic lupus erythematosus: an imbalance of damage and repair?. Trans Res. 2009;154 (2):61-6
8. Schattner A. The cardiovasculer burden of lupus. Arch intern med. 2003;163:1507-10
9. Peripheral arterial disease. Dalam: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editor. Harrison's principle of internal medicine. Edisi 17. New York: McGraw-Hill; 2008:243
10. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease. Morbidity and mortality implications. Circ. 2006;114:688-99
11. Theodoridou A, Bento L, D'Cruz DP, Khamashta MA, Hughes GRV. Prevalence and associations of an abnormal ankle-brachial index in systemic lupus erythematosus: a pilot study. Ann Rheum Dis. 2003;62:1119-1203
12. Burgos PI, Vila LM, Reveille JD, Alarcon GS. Peripheral vascular damage in systemic lupus erythematosus: data from LUMINA, a large multi-ethnic U.S cohort (LXIX). Lupus. 2009;18:1303-8
13. Bhatt SP, Handa R, Gulati GS, Sharma S, Pandey RM, Anggarwai P, et al. Peripheral vascular disease in systemic lupus erythematosus. Lupus. 2007;16:720-3
14. Wang CR, Chou CC, Hsieh KH, Chuang CH, Chen CY. Lupus patient with peripheral vascular thrombosis: the significance of measuring anticardiolipin antibody. Am J Emerg Med. 1993;11:468-70
15. Sari RM, Prevalensi Kejadian Ateroskleoris dan Korelasi antara Faktor Risiko Aterosklerosis terhadap Tebal Kompleks Intima Media Arteri Karotis Penderita Lupus Eritematosus Sistemik (LES) Wanita yang Berusia di bawah 40 Tahun [Tesis]. Jakarta: Universitas Indonesia; 2009.

16. Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. Angiology. 1995;46:211–9
17. Liu A, Zhang W, Tian X, Zhang X, Zhang F, Zeng X. Prevalence, risk factors and outcome of digital gangrene in 2684 lupus patients. Lupus. 2009;18:1112-18
18. Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, dkk. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N engl J Med. 2003;349:2399-406
19. Kahlenberg JM, Kaplan MJ. The interplay of of inflammation and cardiovascular disease in systemic lupus erythematosus. Arthritis research & therapy. 2011;13:203-13
20. McMahoon M, Grossman J. Pathogenesis of atherosclerosis in Lupus. Dalam: JW Daniel, HH Bevr, eds. Dubois Lupus Erythematosus. Edisi 7. Philadelphia. Lipincott Williams&Wilkins;2007:356-66
21. Norman PE, Eikelboom JW, Hankey GJ. Peripheral arterial disesase: prognostic significance and prevention of atherothrombotic complications. MJA. 2004;181:150-4
22. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asimptomatik peripheral arterial disesase is independently associated with impaired lower extremity functioning. The women's health and aging study. Circ. 2000;101:1007-12
23. Hooi JF, Kester ADM, Stoffers HEJH, Rinkens PELM, Knottnerus JA, VanRee JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovasculer morbidity and mortality in a 7-year follow-up study. Journal of clin epid. 2004;57:294-300
24. Petri M, Lakatta C, Magder L, Goldman D. Effect of prednison and hydroxychloroquine on coronary artery disease risk factor in systemic lupus erythematosus: a longitudinal data analysis. Am J Med. 1994;96:254
25. McDonald J, Stewart J, Urowitz MB, Gladman DD. Peripheral vascular disease in patients with systemic lupus erythematosus. Ann Rheum Dis. 1992;51:56-60
26. Willenberg T, Diehm N, Zwahlen M, Kalka C, Do DD, Gretener S, dkk. impact of long-term corticosteroid therapy on the distribution pattern of lower limb atherosclerosis. Eur J Vasc Endovasc Surg. 2010:39;441-6