

Cardiovascular Risk Factors among Patients with Systemic Lupus Erythematosus Presented in a Tertiary Care Hospital

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Abstract

Background : Risk factors for cardiovascular disease are particular habits, behaviors, circumstances or conditions that increase a person's risk of developing cardiovascular disease, including lack of exercise, unhealthy eating, smoking, diabetes, age and family history. Cardiovascular risk factors were observed and compared to find out their contribution among patients with SLE.

Materials and methods : In this case control study, consecutive patients with SLE attending the Department of Medicine Dhaka Medical College Hospital (DMCH) were studied. The control population was recruited from subjects attending the other departments of the hospital and healthy attendants. The prevalence of classic Framingham cardiovascular risk factors, lipid profile, other metabolic risk factors, lifestyle variables, and demographic characteristics were compared between the 2 groups.

Results : 80 SLE patients and 80 age and sex matched controls were studied. Patients with SLE had significantly high BMI and waist circumference (p_0.012 and p_0.001 respectively). Hypertension, diabetes were significantly more common among the SLE patients (31.29% versus 11.25%, p_0.023 and 13.75% versus 3.75, p_0.03). In comparison with control, patients with SLE had no significant difference in mean total cholesterol (193.92±23.65 versus 183.66±11.39, p_0.41) and triglyceride (174.77±60.06 versus 149.15±28.68, p_0.11), but had significantly higher low density lipoprotein (120.77±16.07 versus 108.17±11.68, p_0.00) and lower high-density lipoprotein cholesterol (41.37±4.52 versus 43.51±3.34, p_0.00).

Conclusion : Patients with SLE have a range of detectable and significant cardiovascular risk factors.

Key words : BMI (Body Mass index); CVD (Cardiovascular disease); SLE (Systemic lupus erythematosus).

Introduction

Systemic Lupus Erythematosus (SLE, 'lupus') is a rare autoimmune multiorgan connective tissue disease which can be associated with severe mortality and morbidity.¹ Some 90% of affected patients are female and the peak age at onset is between 20 and 30 years.²

The pathogenesis of SLE is incompletely understood but genetic factors play an important role.² Higher concordance is observed in monozygotic twins and the disease is strongly associated with polymorphic variants at the HLA locus.

SLE has diverse clinical features.¹⁻² Symptoms such as fever, weight loss and mild lymphadenopathy may occur during flares of disease activity, whereas others such as fatigue and low-grade joint pains can be constant. 90% of patients presents with arthralgia which is often associated with early morning stiffness. The classic facial 'butterfly rash' is erythematous, raised and painful or itchy, The typical renal lesion is a proliferative glomerulonephritis, characterised by heavy haematuria, proteinuria and casts on urine microscopy. This increases overall morbidity and mortality.³ Most common cardiovascular manifestations is pericarditis and myocarditis The risk of atherosclerosis is greatly increased, as is the risk of stroke and myocardial infarction.³

SLE is often associated with considerable morbidity and mortality compared to age and gender matched control. The greatest increase in relative risk is extremely high among young women, who otherwise have a low risk of CHD, although the absolute risk of CHD increases with age, as it does in the general population.⁴⁻¹⁰

The pathogenesis of this accelerated atherosclerosis in SLE is likely multifactorial. Traditional risk factors for atherosclerosis (Diabetes, hyperlipidemia, hypertension, family history of Coronary Heart Disease [CHD] obesity,

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sedentary lifestyle and cigarette smoking) are common among patients with SLE, some of these in part due to the adverse effects of glucocorticoids.¹¹⁻¹⁹ The presence of two or more risk-enhancing disorders (ie, metabolic syndrome) is common among patients with SLE.^{18,191} However, after accounting for the increased CHD risk associated with traditional risk factors, SLE itself and/or its treatment confer the greatest risk for premature CHD.²⁰⁻²²

Over time, the risk profile may change, and continued vigilance is necessary to identify the emergence of modifiable risk factors for CHD. Despite an increasing appreciation of the importance of CVD in SLE, the issue is not properly addressed among the SLE patients in Bangladesh. Early identification and management of cardiovascular risk factors may prevent significant morbidity and mortality. Cardiovascular risk factors were observed and compared to find out their contribution among patients with SLE.

Materials and methods

In this case control study we evaluated 80 SLE patients and 80 age and sex matched control during January 2018 to December 2018 in the Department of Medicine, Dhaka Medical College. Informed written consent was obtained from all participants.

Inclusion criteria:

Diagnosed patients with SLE with age 18 years and above.

Exclusion criteria:

SLE with known stroke, Ischemic heart disease, chronic kidney disease, chronic liver disease, dyslipidemia, diabetes, pregnancy. Those patients who were receiving treatment with corticosteroids, statin or antimalarial drugs at the time of this study or within the past 6 months, and patients with known renal impairment (Creatinine 1.1 mg/dl) or significant proteinuria (1 on dipstick analysis or 500 mg/day) were also excluded.

After ethical approval for this study from University of Dhaka, all patients (Admitted, visited in OPD and SLE clinics) in Department of Medicine were screened for selection of case and control.

The subjects were thoroughly informed and written consent were taken.

As part of the routine laboratory assessment, the following parameters was measured : Hemoglobin levels (Hb) Erythrocyte Sedimentation Rate (ESR) C-reactive Protein (CRP) serum creatinine levels, urine routine examination, fasting plasma glucose levels, ANA and Anti ds DNA. Routine clinical samples (Blood, Urine, Chest Xray and ECG) was done on day 2 of admission. Among those Hb level and ESR were done by SYSMEX automated cell counter. Urine R/E were done by BIOTEK analyser, Fasting plasma glucose and serum creatinine were done by 3000 EVOLUTION semiautomatic biochemistry analyzer (China). ANA and anti ds DNA were done by ELISA method.

For lipid sub fractions blood were obtained for laboratory analyses at day 2 of admission and at least 12-hour fast. The plasma and its sub fractions were then aliquoted and stored at 70oC until analyzed in batches. Levels of total cholesterol and TGs were measured in plasma using commercially available assay kit (RANDOX UK). Lipoproteins were separated from plasma into sub fractions: Svedberg flotation (Sf) rates will be (Sf 12) for LDL and HDL during ultracentrifugation. HDL and LDL were separated from each other by manganese chloride/heparin precipitation of LDL from the Sf₁₂ sub fraction. The concentration of HDL was calculated by subtraction of the LDL value from the Sf₁₂ sub fraction.

Statistical analysis was performed with SPSS (Version 21). Data were processed as mean , standard deviation and percentages (Numbers) when appropriate. The variables are compared using the Student's t-test for the continuous variables and the chi-square test for the categorical variables.

Results

Table 1 Comparison of Framingham risk factors between patients with systemic lupus erythematosus (SLE) and controls*

Framingham CV Risk factors	SLE (n = 80)	Controls (n = 80)	OR (95% CI)	p
Hypertension	25 (31.29)	9 (11.25)	2.92 (1.16-7.33)	0.023
Diabetes Mellitus	11 (13.75)	3 (3.75)	4.92 (1.20-20.06)	0.031
Current smoker	1 (1.25)	2 (2.5)	1.36 (0.07-25.24)	0.821
Total Cholesterol (>200mg/dl)	20 (25)	3 (3.75)	7.52 (2.02-28.02)	0.003
HDL cholesterol (<40mg/dl)	31 (38.75)	11 (13.75)	0.32 (0.14-0.77)	0.010
Family history of CAD	16 (20)	11 (13.75)	1.11 (0.42-2.95)	0.825

*Except where indicated otherwise , values are the no.(%) of subjects.

OR= Odds Ratio, 95% CI = 95% Confidence Interval, NS = Not Significant, HDL =high-density lipoprotein, CAD = Coronary Artery Disease.

As shown in Table I, Patients with SLE were more likely to have hypertension (p=0.02) and diabetes mellitus (p=0.03). Significant number of SLE patients were presented with high total cholesterol (p=0.003) and low HDL concentration (p=0.01).

Table II Comparison of BMI & waist circumference between patients with SLE and healthy controls*

Risk factors	Case (n=80)	Control (n=80)	OR (95% CI)	p
BMI				
(Mean ± SD)	28.57±2.94	25.63±2.07	1.29 (1.00-1.66)	0.045
% with >25 kg/m ²	88.9	60.5	3.54 (1.34-9.35)	0.012
Waist circumference				
(Mean ±SD)	81.54±5.90	74.61±5.93	1.10 (0.99-1.21)	0.061
% with >80 cm ²	60.5	23.5	3.44 (1.60-7.25)	0.001

*Except where indicated otherwise, values are the mean ± SD, OR= Odds Ratio, 95% CI=95% Confidence Interval, BMI= Basal Metabolic Index.

Both BMI and waist circumference were significantly higher in patient group (p=0.012 and p=0.011 respectively).

Table III Levels and frequency of lipid subfractions in patients with systemic lupus erythematosus and controls.*

Risk factors	Case (n=80)	Control (n=80)	OR (95% CI)	p
Total cholesterol				
Mean ± SD	193.92±23.65	183.66±11.39	-	0.41
% with > 200mg/dl	25	3.8	3.95 (0.99-15.73)	0.05
LDL cholesterol				
Mean ± SD	120.77±16.07	108.17±11.68	-	0.00
% with >130mg/dl	23.5	7.5	2.61 (0.86-7.90)	0.08
HDL cholesterol				
Mean ± SD	41.37±4.52	43.51±3.34	-	0.00
% with < 40 mg/dl	38.3	13.8	0.33 (0.14-0.77)	0.01
Triglyceride				
Mean ± SD	174.77±60.06	149.15±28.68	-	0.11
% with > 150 mg/dl	46.9	20	2.27 (1.04-4.93)	0.03

* Except where indicated otherwise, values are the mean ± SD. RR=Relative Risk, 95% CI = 95% Confidence Interval, NS = Not Significant, LDL= Low-Density Lipoprotein, VLDL = Very Low-Density Lipoprotein, HDL =High-Density Lipoprotein.

Table III shows, mean total cholesterol and triglyceride levels were comparable in the 2 groups, But SLE patients had significantly higher levels of mean LDL cholesterol and low HDL level (p=0.00 and p=0.00 respectively). Significant number of patients with SLE had high total cholesterol, hypertriglyceridemia and low HDL.

Table IV Association with characteristics of patients with SLE (n =80) and lipid abnormality*

Characteristics of SLE patients (n=80)	Cholesterol (>200 mg/dl)	LDL (>130 mg/dl)	HDL (<40 mg/dl)	TG (>150 mg/dl)
Duration SLE >5yr	0.14	0.20	0.63	0.42
High BMI >25	0.389	0.93	0.93	0.03
Waist cir >80	0.04	0.07	0.34	0.00
SLEDAI >6	0.57	0.68	0.88	0.43
Steroid use > 3yr	0.00	0.01	0.42	0.00
Antimalarial use	0.24	0.27	0.54	0.39

*Values are p value. LDL= Low Density Lipoprotein, HDL = High Density Lipoprotein, TG= Triglyceride, BMI= Basal Metabolic Index, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

Only high waist circumference (>80 cm) and steroid use (> 3 year) were found to be significantly associated to altered serum total cholesterol and triglyceride. Duration of disease (>5years), BMI (>25), SLEDAI (>6) and antimalaria drug use had no significant effect on patients lipid profile.

Discussion

As the prognosis of SLE has improved, accelerated atherosclerosis and premature CHD have become increasingly recognized as significant late complications. Several studies have confirmed that patients with SLE have a 5–8-fold increased risk of CHD-related events compared with the general population.^{17,20} Several cardiovascular risk factors are related to these early cardiovascular events in SLE.

With regard to the Framingham cardiovascular risk factors currently utilized in assessing the risk of CHD for primary prevention purposes. It was found that, SLE patients in this study were more likely to have hypertension, diabetes mellitus, hypercholesterolemia and low HDL cholesterol. These 4 factors (Hypertension, hypercholesterolemia and low HDL) contributed to the overall increased mean number of Framingham factors present in the SLE patients as compared with the controls. Patients with SLE and CHD had one less risk factor than did a control cohort of individuals with accelerated CHD but without SLE.²³ This finding confirms the results of a prior study by Esdaile et al, who noted that even after adjusting for the presence of Framingham risk factors at baseline, the risk of CHD in lupus patients was still increased by a factor of 8 compared with that in the population controls.²⁰

Differences in the levels of lipid sub fractions were also observed between patients and controls. Whereas mean total cholesterol and triglyceride levels were comparable in the 2 groups, SLE patients had significantly higher levels of mean LDL cholesterol and low HDL level. Significant number of patients with SLE had high total cholestroemia, hyper triglyceridemia and low HDL. Several previous studies have described a dyslipoproteinemia associated with active SLE that is characterized by increased TGs, increased VLDL cholesterol, and reduced HDL cholesterol.²⁴

Steroid therapy is also known to increase the levels of LDL cholesterol and TGs.^{21,24} In this study steroid intake were found to be significant to cause hypercholesterolemia, hypertriglyceridemia and low HDL. Antimalarial use (Hydroxychloroquine) was not found to be significant in lipid alteration. Lipid-lowering effect of antimalarial drugs that may also be of relevance in this setting.^{25,26} Disease activity measured by SLEDAI to all patients. It is found that mean SLEDAI is not significantly correlated to alter mean level of lipid subfraction.

The changes in total cholesterol and TGs may both be related to the increased waist circumference observed in the patient group. They may also reflect a combination of ongoing inflammation and the influence of steroid therapy. It is suggested that TGs and LDL cholesterol may be a more important risk factor in women than in men.^{27,28}

This is the first case-control study of its kind. It was noted, significant differences in the risk factor profile of patients with SLE compared with healthy controls in the areas of demographics, lifestyle, traditional risk factors, and more novel CHD risk factors. Overall, patients with SLE have more of these risk factors than do individuals in the general population. Some study previously demonstrated that sustained lipid abnormality and hypertension are risk factors for CHD-related events and mortality in patients with SLE. So many of these risk factors may contribute to the increased risk of CHD observed in SLE.

It will, however, require a large prospective study to determine the relative contribution of each of these factors to the incidence of CHD in SLE in Bangladesh. Many of the factors identified are potentially amenable to screening and intervention. They may also be amenable to better long-term

control of the underlying inflammatory process. As such, careful control of disease activity and a proactive policy of screening patients with SLE for potentially modifiable risk factors seem appropriate.²⁹

Limitations

- Small sample size (Case 80 and control 80).
- The study was conducted in a single tertiary care center.
- Novel cardiovascular risk factors i.e. Homocysteine, Fibrinogen level, LDL size, Apo E-4, RBC folate and condition of coronary artery could not be studied due to lack of resource.

Conclusion

This study identifies that, patients with systemic lupus erythematosus are at a high risk for developing cardiovascular disease. Therefore, it is important for clinicians to carefully monitor disease activity and proactively screen for potentially modifiable risk factors. Additionally, further research is needed to understand the contribution of the inflammatory process to CHD risk in this population.

Recommendations

To prevent early cardiovascular event in patients with SLE following measures can be taken during management though further study is needed to recommend as a guideline.

- Education about early cardiovascular event can improve patients outcome.
- Lifestyle intervention should be discussed to all patients.
- Screening for cardiovascular risk factors should be included in regular follow up programme of SLE.

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Contribution of authors

HH-Conception, design, acquisition data, interpretation of data, drafting and final approval.

MSA-Design, interpretation of data, critical revision and final approval.

MAI-Acquisition data, interpretation of data, critical analysis and final approval.

ATMMC-Interpretation of data, critical analysis and final approval.

Disclosure

All authors declared no conflict of interest.

Reference

1. Ward MM, Pyun E, Studenski S. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. *Arch Intern Med.* 1996; 156:1337.
2. Stuart H, Ralston, Ian D, Penman, Mark W.J, Strachan, Richard P, Hobson. *Systemic lupus erythematosus, Davidson's Principles and Practice of Medicine: 23rd edition: Elsevier,USA.* 2018;24:1034 .
3. Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res (Hoboken).* 2014; 66:608.
4. Rubin LA, Urowitz MB, Gladman DD. Mortality in systemic lupus erythematosus: the bimodal pattern revisited. *Q J Med.* 1985; 55:87.
5. Jonsson H, Nived O, Sturfelt G. Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine (Baltimore).* 1989; 68:141.
6. Reveille JD, Bartolucci A, Alarcón GS. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. *Arthritis Rheum.* 1990; 33:37.
7. Petri M, Spence D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine (Baltimore).* 1992; 71:291.
8. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol.* 1997; 145:408.
9. Hak AE, Karlson EW, Feskanich D, et al. Systemic lupus erythematosus and the risk of cardiovascular disease: Results from the nurses' health study. *Arthritis Rheum.* 2009; 61:1396.
10. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: A systematic review. *Semin Arthritis Rheum.* 2013; 43:77.
11. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med.* 1992; 93:513.
12. Asanuma Y, Oeser A, Shintani AK, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med.* 2003; 349:2407.
13. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med.* 2003; 349:2399.
14. Wierzbicki AS. Lipids, cardiovascular disease and atherosclerosis in systemic lupus erythematosus. *Lupus.* 2000; 9:194.
15. Li D, Yoshida K, Feldman CH, et al. Initial disease severity, cardiovascular events and all-cause mortality among patients with systemic lupus erythematosus. *Rheumatology (Oxford).* 2020; 59:495.
16. Bruce IN, Gladman DD, Urowitz MB. Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am.* 2000; 26:257.
17. Bruce IN, Urowitz MB, Gladman DD, Hallett DC. Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol.* 1999; 26:2137.
18. Zonana-Nacach A, Santana-Sahagún E, Jiménez-Balderas FJ, Camargo-Coronel A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. *J Clin Rheumatol.* 2008; 14:74.
19. Bultink IE, Turkstra F, Diamant M, et al. Prevalence of and risk factors for the metabolic syndrome in women with systemic lupus erythematosus. *Clin Exp Rheumatol.* 2008; 26:32.
20. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum.* 2001; 44:2331.
21. Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. *Am J Med.* 1994; 96:254.
22. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *Am J Epidemiol.* 2012; 176:708.
23. Rahman P, Urowitz MB, Gladman DD, Bruce IN, Genest J Jr. Contribution of traditional risk factors to coronary artery disease in patients with systemic lupus erythematosus. *J Rheumatol.* 1999; 26:2363–2368.
24. Ilowite NT, Samuel P, Ginzler E, Jacobson MS. Dyslipoproteinemia in pediatric systemic lupus erythematosus. *Arthritis Rheum.* 1988;31:859–863.

- 25.** Wallace DJ, Metzger AL, Stecher VJ, Turnbull BA, Kern PA. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. *Am J Med.* 1990;89:322–326.
- 26.** Rahman P, Gladman DD, Urowitz MB, Yuen K, Hallett D, Bruce IN. The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. *J Rheumatol.* 1999;26:325–30.
- 27.** Korhonen T, Savolainen MJ, Koistinen MJ, Ikaheimo M, Linnaluoto MK, Kervinen K, et al. Association of lipoprotein cholesterol and triglycerides with the severity of coronary artery disease in men and women. *Atherosclerosis.* 1996;127:213–220.
- 28.** Gotto AM Jr. Triglyceride as a risk factor for coronary artery disease. *Am J Cardiol.* 1998;82:22–50.
- 29.** Bruce IN, Gladman DD, Urowitz MB. Detection and modification of risk factors for coronary artery disease in patients with systemic lupus erythematosus: A quality improvement study. *Clin Exp Rheumatol.* 1998;16:435–440.