Research Article

Cardiovascular risk factors and carotid atherosclerosis in patients with systemic lupus erythematosus at Kenyatta National Hospital

Shiruli BC[1], Oyoo GO[1], Ogola EN[1], Amayo EO[1], Aywak AA[2]

[1]Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, Kenya
[2]Department of Diagnostic Radiology, College of Health Sciences, University of Nairobi, Kenya

Corresponding author:
Dr. BC Shiruli. Email: cheroshiruli@yahoo.com

Abstract

***Background*:** Cardiovascular disease is now acknowledged as a primary cause of morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). The risk of developing coronary artery disease in these patients is four to eight times higher than that in the normal population. Prior to this study there was no data regarding cardiovascular risk in SLE patients in our setting.

***Objective*:** To determine the prevalence of selected cardiovascular risk factors and carotid atherosclerosis in patients with systemic lupus erythematosus at Kenyatta National Hospital.

***Methods*:** This was a cross-sectional survey carried out in patients with SLE and age- and sex-matched controls at the Kenyatta National Hospital. The SLE patients underwent clinical assessment of their blood pressure, weight, height, waist and hip circumferences as well as laboratory testing to determine their fasting blood sugar and fasting lipid profile. In addition, measurement of carotid Intima-Media Thickness (IMT) and assessment for presence of carotid plaque was done for the lupus patients. The controls had similar clinical and laboratory assessment done as for patients. Carotid ultrasonography was however not done for controls.

Results: Sixty six SLE patients and 66 healthy controls participated in this study. Mean age of the patients was 35.9 years, with a female to male ratio of 21:1 and median duration of illness of two years. Hypertension prevalence was 42.4% in the patients and 24.2% in the controls (p=0.027), dyslipidemia occurred in 74.2% of the patients and 62.1% of the controls (p=0.135) while diabetes prevalence was 4.5% in patients and 1.5% in controls (p=0.619). Obesity by Body Mass Index (BMI) assessment was found in 12.1% of patients and 21.2% of the controls (p=0.330) whereas abdominal obesity (by waist: hip ratio) occurred in 33.3% of patients and 24.2% of controls (p=0.249). Mean carotid IMT in SLE patients was 0.63mm (SD=0.15) with 9 (13.6%) patients having IMT readings of 0.8mm and above. Carotid plaque was detected in 15 (22.7%) patients. Carotid IMT and BMI significantly correlated with disease duration (p values= 0.006 and 0.021 respectively).

Conclusion: There was a high prevalence of atherosclerosis and selected cardiovascular risk factors in this population of SLE patients. Hypertension was significantly more common in the lupus patients than controls. Cardiovascular risk assessment and appropriate treatment of risk factors identified should be enhanced in patients with SLE.

Key words: Systemic lupus erythematosus, Cardiovascular risk factors, Carotid intima-media thickness, Carotid plaque

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease whose reported prevalence in different parts of the world ranges from 20-150 cases per 100,000[1,2]. It has been reported to occur infrequently among blacks in Africa[3]. Median age at diagnosis tends to be in the early thirties as shown in studies in Africa; 33 years in Nigeria[4] and 34 years in South Africa[5]. Lupus is known to occur predominantly in females worldwide.

Risk of death in lupus patients is two to five times higher than that in the general population, with a bimodal pattern of mortality described. Early mortality (less than one year since diagnosis) has been associated with severe disease activity while later mortality tends to be secondary to complications of longstanding disease and treatment options used in controlling the illness[6,7]. Accelerated atherosclerosis and consequent cardiovascular disease contributes to the causes of late mortality in these patients[8]. Furthermore, in comparison to other races, black women with lupus have been shown to die of cardiovascular disease much earlier than sex- and race-matched controls.[9] Whereas the pathogenesis of accelerated atherosclerosis in these patients is still incompletely understood, three contributing factors have been well described. These include the inflammatory

nature of SLE, the higher burden of traditional cardiovascular risk factors and the use of corticosteroids which are pro-atherogenic[10].

In the INTERHEART study, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, inadequate consumption of fruits and vegetables, alcohol intake, psychosocial factors and sedentary lifestyle (commonly referred to as the traditional cardiovascular risk factors) accounted for over 90% of the risk of myocardial infarction in the general population[11]. In the John Hopkins lupus cohort, 53% of the SLE patients had three or more of the classic cardiovascular risk factors[12] while in the Toronto Risk Factor study, hypertension, diabetes, elevated triglycerides and elevated low density lipoprotein were significantly more common in the lupus patients than controls[13]. This increased prevalence of cardiovascular risk factors in these patients means their risk of coronary disease is higher than that in the general population. Another important factor is the chronic inflammation that occurs in SLE. Chronic inflammation is central in the pathogenesis of atherosclerosis which begins with endothelial injury. A number of factors inherent in SLE such as autoantibody formation, impaired immune clearance, complement activation, elevated homocysteine levels among others contribute to endothelial injury and ultimately to atherogenesis[14]. Steroid therapy in lupus patients has been associated with an increase of traditional cardiovascular risk factors and atherosclerosis[15,16].

This study sought to assess the burden of selected cardiovascular risk factors and carotid atherosclerosis (as a marker of atherosclerotic disease) in SLE patients at Kenyatta National Hospital with the aim of providing a basis for primary and secondary interventions to reduce cardiovascular morbidity and mortality in the population.

Materials and Methods

This was a cross-sectional survey in SLE patients and controls at the Kenyatta National Hospital. The SLE patients were above 18 years of age and fulfilled the ACR criteria for diagnosis of lupus[17]. They were recruited into the study at the Rheumatology Out-Patient clinic, the Renal Clinics and the medical wards over a period of nine months. Controls were staff and students at the institution who were sex- and age-matched (to the nearest 5 years) to the SLE patients in the study. They were screened to exclude symptoms of SLE in the present or past.

The SLE patients and the controls had anthropometric measurements taken to assess for obesity as per WHO guidelines. Blood pressure readings were taken and hospital records assessed to determine those who were hypertensive. The patients and controls also had fasting blood sugar and fasting lipid profile assays done. Bilateral carotid ultrasonography was subsequently performed on the SLE patients by a team of consultant radiologists to evaluate for the presence of carotid plaque and for Carotid Intima-Media Thickness (CIMT) measurement. Carotid plaque was defined as the presence of focal wall thickening that was at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT greater than 1.5millimeters that protruded into the lumen from the adjacent boundary. Mean maximum CIMT was derived using images from all the carotid artery segments bilaterally; including the common carotid artery, carotid bulb and the internal carotid artery. Carotid atherosclerosis definition was the presence of carotid plaque and/ or an abnormal CIMT reading (≥0.8mm).

Data collected was coded, entered and managed in a pre-designed Microsoft Access database. Data entry was done continuously during the research period and data cleaning performed at the end of entry. After the data was cleaned, it was exported to the SPSS version 17.0 software for analysis. Demographic and clinical characteristics of the patients were summarized into means, medians and proportions for continuous and categorical variables respectively. Prevalence findings for carotid atherosclerosis (abnormal CIMT and carotid plaque presence) and cardiovascular risk factors were analyzed and presented as proportions. Anthropometric measurements were classified as per the World Health Organization (WHO) guidelines and analyzed with prevalence findings for obesity presented as proportions. Prevalence of cardiovascular risk factors in the SLE patients and controls were compared using the chi-square or Fischer's exact tests where appropriate. Comparison of anthropometric measurements between the two groups was done using the Student's t-test. Odds ratios were calculated to estimate the risk among SLE patients as compared to controls. All statistical tests were performed at a 5% level of significance.

Results

Between January and September 2013, a total of 66 SLE patients and 66 healthy controls were recruited into the study. Sixty three (95.5%) SLE patients and a similar number of controls were female; with a female to male ratio of 21:1. Mean age of the patients was 35.9 years (±10.9SD) and 35.7 years (±10.2SD) for the controls. Fifty percent of the patients and a similar proportion of controls were married. Median duration of illness for SLE patients was 2 years and the mean age at diagnosis 33.1 years. Only one of the SLE patients had confirmed secondary antiphospholipid antibody syndrome. A total of 58 of the 66 patients (87.9%), took steroids regularly as part of their treatment. Of these most (55.2%) were on a prednisone dosage of 10–20 milligrams per day. Nearly half of the patients (31 of the 66), were on treatment with either methotrexate, azathioprine, mycophenolate mofetil or a combination of the immunosuppressants. Only one patient was on a statin and another four were on anti-platelet agents (aspirin or clopidogrel).

Carotid atherosclerosis occurred in 19 (28.8%) of the 66 lupus patients. Nine patients (13.6%) had abnormal CIMT and carotid plaque(s) was found in 15 (22.7%) patients.

Twenty eight patients (42.4%) with lupus had hypertension compared with 16 (24.2%) controls and the difference was statistically significant {O.R. 2.3, CI: (1.1-4.9), p-value = 0.027}. Dyslipidemia occurred in 49 (74.2%) SLE patients and 41(62.1%) of the controls (p-value = 0.135). Twenty two patients (33.3%) and 23 (34.8%) controls had elevated total cholesterol levels (p-value=0.078); hypertriglyceridemia occurred in 36.4% of patients and 27.3% of controls (p-value= 0.350); risk indicator levels of HDL were found in 50% of patients and 34.8% of controls (p-value=0.078) while elevated LDL levels occurred in 30.3% of both patients and controls. Three patients and one control had diabetes. There was no statistically significant difference in the occurrence of obesity in lupus patients compared to controls. Among the SLE patients, 12.1% had obesity as per the WHO BMI classification compared with 21.2% of controls. Twelve (18.2%) of SLE patients were underweight (i.e. with BMI<18.5) compared to only two controls and this was significant; p-value = 0.010. Abdominal obesity as assessed by the waist to hip ratio was more frequent among the patients (33.3%) than the controls (24.2%) but this difference was not significant (p-value = 0.249) (Table 1).

A total of six SLE patients (9.1%) had already had a cardiovascular event(s) in the past; one patient had both stroke and myocardial infarction in the previous 2 years, another patient had stroke only, and four patients had experienced angina.

Table 1: Cardiovascular risk factors in SLE patients and healthy controls

Variable	SLE patients (n=66) No. (%)	Controls (n=66) No. (%)	OR (95% CI)	P-value
Hypertension	28 (42.4)	16 (24.2)	2.3 (1.1 - 4.9)	0.027
Dyslipidemia	49 (74.2)	41 (62.1)	1.8 (0.8 – 3.7)	0.135
Diabetes	3 (4.5)	1 (1.5)	3.1 (0.3 – 30.6)	0.619
Obesity by BMI BMI ≥ 30	8 (12.1)	14 (21.2)	0.6 (0.2 – 1.7)	0.330
Obesity by W:H ratio Females ≥ 0.85 Males ≥ 0.90	22 (33.3)	16 (24.2)	1.6 (0.7 – 33)	0.249
Obesity by waist circumference Females >80cm Males >94cm	22 (33.3)	27 (40.9)	0.7 (0.4 – 1.5)	0.368

Table 2: Carotid intima media thickness and carotid plaque in SLE patients

Variable	Frequency / Value
Mean CIMT(millimeters)	
Mean (SD)	0.63 (0.15)
Min - Max	0.35 -1.06
CIMT Status	
Normal (<0.8mm)	57 (86.4%)
Abnormal (≥ 0.8mm)	9 (13.6%)
Presence of carotid plaque	
Present	15 (22.7%)
Absent	51 (77.3%)

Three male SLE patients were on follow-up at the rheumatology clinic at the time of the study. None of these men (mean age of 34 years) were hypertensive, diabetic or obese. Two of the three had dyslipidemia, one had an abnormal CIMT (≥0.8mm) and another had carotid plaque (Table 2).

Lupus patients with carotid atherosclerosis and obesity had significantly longer duration of illness compared to those without these findings (p-values = 0.040 and 0.021 respectively). Analysis to assess for correlation between carotid atherosclerosis and the use of corticosteroids or other immunosuppressants and the traditional cardiovascular risk factors did not yield any significant findings. Similarly there was no statistically significant correlation between the presence of traditional cardiovascular risk factors and regular use of steroids or other immunosuppressants.

Discussion

This study population consisted predominantly of young females in the reproductive age group with a relatively short median duration of SLE (2 years since diagnosis). The mean age at diagnosis of lupus was 33.1 years with a female to male ratio of 21:1. Other studies within the African continent have had similar findings such as a mean age at diagnosis of 33 years and female to male ratio of 21:1 in Nigeria[4] and mean age of 33 years at diagnosis in a South African study with a female to male ratio of 18:1[5].

The prevalence of hypertension in this study was 42.4% amongst the lupus patients and 24.2% in the controls with the difference being of statistical significance (p=0.027). Vascular stiffness has been associated with the inflammatory process in SLE and is thought to contribute to the higher rates of hypertension in lupus patients than the general population[18]. Other factors that have been associated with hypertension in these patients include lupus nephropathy and steroid intake[19, 20]. This study neither assessed for level of inflammation nor evaluated for lupus nephropathy and thus such correlations could not be pursued. It is however notable that up to 87.9% (58 out of 66) of SLE patients used corticosteroids on a regular basis. Probably due to the fact that almost all the patients were on steroids no correlation was shown between regular intake of steroids and hypertension or other study variables. In the Toronto Risk Factor Study, hypertension occurred in 33% of the lupus patients compared with 13% in the controls[13] while 41% in the John Hopkins Lupus cohort were hypertensive[12].

Dyslipidemia occurred in about three quarters of SLE patients (74.2%) compared to 62.1% of the controls (p=0.135). A third of the lupus patients (33.3%) had hypercholesterolemia, 50% had low HDL levels, 30.3% had elevated LDL and 36.4% had hypertriglyceridemia. Only one patient was on a statin, indicating that dyslipidemia in this group was largely untreated. These findings were similar to those in a study that evaluated the proportions of dyslipidemia in SLE patients in Indonesia[21]. In that study, dyslipidemia prevalence was 75% with hypercholesterolemia in 43%, low HDL in 26%, elevated LDL in 26.4% and raised triglycerides in 44.2%. Of note, all the patients in that study were on corticosteroids and lupus duration less than three years correlated with dyslipidemia prevalence. No association between steroid use and dyslipidemia was demonstrated in our SLE patients, majority of whom used the corticosteroids regularly. It was also observed that a big proportion (62.1%) of controls who were staff or students at the Kenyatta National Hospital had dyslipidemia. An earlier study by Kirui *et al*[22] that assessed the prevalence of cardiovascular risk factors in rheumatoid arthritis patients and healthy staff at our institution as controls found 73.8% of the control population to have dyslipidemia. This raises concern that this population probably has some undescribed characteristics that may put them at risk of dyslipidemia and thus cardiovascular disease.

Diabetes was not a frequent finding in the study population. Three (4.5%) of the lupus patients and one control were diabetic. All the three patients had recently been hospitalized and were on high doses of prednisone, above 20 milligrams per day which may have contributed to their hyperglycemic states. Other studies have found similar proportions of diabetics among lupus patients. In the Toronto Lupus cohort, 5% were diabetic[13] comparable to 7% in the John Hopkins lupus cohort[12].

Obesity defined as BMI ≥ 30, occurred in eight (12.1%) of our patients and 14 (21.2%) of the controls and correlated with longer disease duration in the SLE patients. Abdominal obesity which has been strongly associated with cardiovascular disease[11], occurred almost similarly in the lupus patients (33.3%) and controls (24.2%). About a fifth (18.2%) of the lupus patients were actually underweight (BMI <18.5) compared to only 3% of controls (p=0.011) which may point to active disease rather than stable chronic disease in that proportion of our patients. The association between obesity and longer disease duration may be attributable to longer exposure to steroids and possible reduction in physical activity that may occur in these patients especially those with musculoskeletal involvement. In the John Hopkin's lupus cohort, 38% of patients were obese and 70% had a sedentary lifestyle while 15.6% in the Toronto Risk Factor study had abdominal obesity[12,13]. Variation in obesity prevalence in these studies is partly due to use of different cut-offs to define obesity.

Prevalence of carotid atherosclerosis in this study was 28.8%. Carotid plaque(s) occurred in 22.7% of the patients and abnormal CIMT in 13.6% of the lupus patients. In a study that assessed for the prevalence and correlates of accelerated atherosclerosis in SLE patients in New York, Roman *et al*[23] found a higher prevalence of carotid plaque, occurring in 37.1% of the patients whose mean age was 44 years with a mean duration of illness of 10.75 years. Another study in British women with SLE that sought to evaluate the health-related quality of life, smoking and atherosclerosis found carotid plaque in 26%

of the patients and abnormal CIMT (cut-off >0.51mm as per studies in their general population) in 35% of the patients whose mean age was 47.6 years and mean duration of illness 11.4 years[24]. Our study population therefore had lower rates of carotid plaque and abnormal CIMT than those in the aforementioned studies and this was probably a consequence of our lupus patients being younger and having had the disease for shorter duration than those in the other two studies.

Carotid atherosclerosis was associated with a longer duration of illness, a finding that was also observed in the study by Roman *et al*[23] and in a more recent study that assessed the progression of carotid atherosclerosis in SLE patients[25]. Whereas longer disease duration also results in advancing of age which is known to be associated with progression of atherosclerosis in the general population, the above two studies found longer disease duration independently correlated with carotid atherosclerosis.

A total of six patients (9.1%) in this study already had a cardiovascular event; one patient had both stroke and myocardial infarction in the previous two years, one patient had stroke only and another four patients had experienced angina. These findings in a population with a relatively short duration of SLE affirm the need to pay attention to cardiovascular risk in our patients.

Conclusion

Patients with SLE had a high prevalence of atherosclerosis. Hypertension was more common in these patients than the controls. Both the lupus patients and the controls had high prevalence of dyslipidemia. There was no significant difference in the occurrence of diabetes, dyslipidemia and obesity in the SLE patients and controls.

Study limitations

Due to financial constraints, comparison of atherosclerosis in SLE patients and controls was not done. It is acknowledged that doing so would have given more information on cardiovascular risk in patients with lupus. Furthermore, disease activity and damage scores were not established for the patients thus assessment for correlation of atherosclerosis and traditional cardiovascular risk factors to these parameters could not be done. We also did not evaluate for the presence of lupus nephropathy in the patients.

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