

CARDIOVASCULAR RISK FACTORS AND
CAROTID ATHEROSCLEROSIS IN
PATIENTS WITH SYSTEMIC LUPUS
ERYTHEMATOSUS AT THE KENYATTA
NATIONAL HOSPITAL

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DECLARATION

This dissertation is my original work and has not been presented for a degree in any other university.

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DEDICATION

This dissertation is dedicated to my dear husband Austine. Your support as I have carried out this study and pursued my masters training has been immense and a source of great inspiration. You have always urged me to be my best and I hope I made you proud.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACR	American College of Rheumatology
Anti-DNA	Anti-Deoxyribonucleic acid
Anti-Sm	Anti-Smith Antibodies
BMI	Body Mass Index
CIMT	Carotid Intima-Media Thickness
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-II
DMARDs	Disease Modifying Anti-Rheumatic Drugs
HDL	High Density Lipoproteins
HF	Heart Failure
JNC VII	The 7 th report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure
LDL	Low Density Lipoproteins
MI	Myocardial Infarction
NSAID	Non-Steroidal Anti-inflammatory Drugs
OHA's	Oral Hypoglycemic Agents
SLE	Systemic Lupus Erythematosus
WHO	World Health Organization
WHR	Waist: Hip Ratio

ABSTRACT

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

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. There has been paucity of 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.

Methodology: 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 with measurement of their blood pressure, weight, height, waist and hip circumferences. They also underwent laboratory testing to determine their fasting blood sugar and fasting lipid profile. In addition, carotid Doppler ultrasonography was done for the lupus patients. The controls had similar clinical and laboratory assessment done as for controls. Carotid ultrasonography was however not done for controls.

Results: Sixty six SLE patients and 66 healthy controls participated in this study. The mean age of the patients was 35.9 years, with a female to male ratio of 21:1 and a 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 the prevalence of diabetes was 4.5% in patients and 1.5% in controls ($p=0.619$). Obesity by 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 ($p=0.249$). Carotid atherosclerosis occurred in 19 patients (28.8%) and was associated with longer duration of illness ($p=0.040$). Correlation between obesity (by BMI assessment) and longer disease duration was also found ($p=0.021$).

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.

1.0 LITERATURE REVIEW

1.1 INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease whose reported prevalence in different parts of the world ranges between 20 - 150 cases per 100,000.¹⁻³ The prevalence of SLE is higher among Asians, Afro-Americans, Afro-Caribbeans, and Hispanic Americans compared to Americans of European decent in the United States, and among Asian Indians compared to Caucasians in Britain.⁴⁻⁶ In comparison, SLE occurs infrequently in Blacks in Africa.⁷

Systemic lupus erythematosus, also referred to as lupus, has a predilection for women with female to male ratio peaking at 11:1 during the child bearing years.⁷ In a retrospective study of SLE patients seen at Kenyatta National Hospital between 1972 – 1984, L.S. Otieno et al found a female to male ratio of 30:1 with bimodal peaks at 15–25 and 35 – 45 year age groups.⁹ Onset of SLE is usually after puberty typically in the 20s and 30s, with 20% of all cases diagnosed during the first two decades of life.¹⁰ Mean age at presentation was 33years in SLE patients seen at a rheumatology clinic in Lagos, Nigeria¹¹ and 34years in Soweto, South Africa patients.⁶

Five year survival rates between 57 - 72% were found in South African SLE patients compared to rates above 90% in the industrialized world.^{12 - 14} Risk of death in lupus patients is two- to five-fold that in the general population, with a bimodal pattern of mortality described.^{15 -17} Early mortality (less than one year since diagnosis) is usually related to severe disease activity while later mortality is associated with complications of longstanding disease and treatment with immunosuppressive agents. Infection and accelerated atherosclerosis are causes of late mortality.¹⁸

Although the specific cause of SLE is unknown, multiple factors are associated with development of the disease, including genetic, racial, hormonal and environmental factors.¹⁹⁻²¹ Both innate and acquired immune disturbances occur in lupus patients. Proposed mechanisms include a defect in apoptosis that causes increased cell death and impaired immune tolerance.²⁰⁻

²⁴ Plasma and nuclear antigens are abnormally displayed on the cell surfaces attracting autoimmune activity by intolerant lymphocytes. Clinical features are a consequence of circulating immune complexes or due to direct effects of antibodies on the cell surface components.

The 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of SLE has been used in diagnosis of lupus. Diagnosis is made when 4 or more of 11 criteria (indicated in table 1 below) are present in an individual.²⁵

Table 1: ACR Revised Criteria for Classification of SLE

	Criteria
Cutaneous	1. Malar rash: fixed malar erythema, flat or raised.
	2. Discoid rash: erythematous raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur.
	3. Photosensitivity: skin rash as an unusual reaction to sunlight; diagnosed by patient history and physician observation.
	4. Oral ulcers: oral or nasopharyngeal ulcers, usually painless; observed by a physician.
Systemic	1. Arthritis: non-erosive, involving ≥ 2 peripheral joints; characterized by tenderness, swelling, effusion.
	2. Serositis: pleuritis (convincing history of pleuritic pain or rub heard by physician, or evidence of pleural effusion) or pericarditis (documented by electrocardiogram, rub, or evidence of pericardial effusion).
	3. Renal disorder: persistent proteinuria (>0.5 grams/day or $>3+$) or cellular casts of any type.
	4. Neurologic disorder: seizures or psychosis in the absence of other causes.
Laboratory	1. Hematologic disorder: hemolytic anemia or leucopenia ($<4000/\text{mm}^3$ on 2 occasions), lymphopenia ($<1500/\text{mm}^3$ on two occasions), or thrombocytopenia ($<100,000/\text{microlitre}$ in the absence of offending drugs).
	2. Immunologic disorder: anti-dsDNA or anti-Sm, or antiphospholipid antibodies (abnormal IgM or IgG anticardiolipin antibody, lupus anticoagulant, or false positive syphilis serology).
	3. Positive Anti-Nuclear Antibody (ANA) in the absence of drugs known to associated with the “drug-induced lupus syndrome.”

The above criteria has been recently validated by the Systemic Lupus International Collaborative Clinics (SLICC) group which also provided an alternative SLICC 2012 criteria for use in SLE clinical care and research.²⁶

1.2 CAUSES OF MORTALITY IN SLE

Patients with SLE have been shown to have a bimodal pattern of mortality. Causes of death in the early years of illness are commonly associated with active disease and infections due to use of high dose steroids and immunosuppressants. Later in the disease, mortality is due to complications of longstanding disease and immunosuppressive therapy. Accelerated atherosclerosis is one such cause of death later in the course of lupus.¹⁷ A prospective twenty year study to establish causes of mortality in Danish lupus patients found death at the beginning of the survival curve to have been related to SLE manifestations and infections. Mortality in the latter part of the study was mainly due to cardiovascular disease and malignancies.²⁷

1.3 SLE AND CARDIOVASCULAR DISEASE

Cardiovascular morbidity and mortality is a frequent complication in patients with SLE. Female patients aged 35 – 44 years were found to have a 50-fold increase in risk for myocardial infarction compared to females of the same age group in the Framingham Offspring Cohort Study.²⁸ A nationwide retrospective analysis of inpatient records in the United States over four years (2003 -2006) established that women with SLE got admitted with a cardiovascular event 10.5years earlier than women in the general population. Furthermore the same study found that among different racial groups with SLE, black women with lupus were 19.8years younger than race- and sex-matched controls at the time of cardiovascular disease-associated death.²⁹

Accelerated atherosclerosis and increased cardiovascular mortality in lupus patients were first described in the 1970's.¹⁷ Despite an incomplete understanding of the pathogenesis, three main contributing factors are now recognized in the aetiology of accelerated atherosclerosis in lupus patients: the systemic inflammatory nature of the disease which plays a role in atherogenesis, the higher burden of traditional cardiovascular risk factors in SLE patients compared to the general population and the use of corticosteroids which are pro-atherogenic.³⁰ Studies have also

demonstrated an association between increased serum creatinine and proteinuria due to lupus nephropathy, and increased cardiovascular risk.^{31, 32}

1.4 AUTOIMMUNE-INFLAMMATORY NATURE OF SLE AND ATHEROSCLEROSIS

Chronic inflammation is a key component in the pathogenesis of both lupus and atherosclerosis. There is growing consensus that atherosclerosis is an immune-mediated process occurring within the vascular system.³³ Endothelial injury is the initial step in atherogenesis which is followed by endothelial dysfunction and inflammatory responses that result in atheromatous plaque formation.³⁴⁻³⁶ Causes of endothelial injury are varied and include shear stress, infectious diseases, homocysteine, autoantibodies, immune complexes, complement activation, oxidative stress among others. Some of these factors such as autoantibody formation, impaired immune complex clearance, complement activation and elevated homocysteine levels occur in the pathogenesis of both SLE and coronary artery disease.^{37, 38} The inflammatory response to endothelial injury involves expression of adhesion molecules within the endothelium and secretion of cytokines to recruit other inflammatory cells. The cytokines induce proliferation of macrophages and smooth muscle cells. The macrophages differentiate and express scavenger receptors, take up oxidized LDL and undergo transformation into foam cells. Subsequently, formation of fatty streaks and atheromatous plaques occurs.³³ Matrix-degrading proteases and tissue factor produced by macrophages eventually lead to plaque rupture and thrombus formation that result in cardiovascular events.³⁴⁻³⁶

1.5 TRADITIONAL CARDIOVASCULAR RISK FACTORS IN SLE PATIENTS

In the INTERHEART study, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, inadequate consumption of fruits and vegetables, alcohol intake, psychosocial factors and sedentary lifestyle accounted for over 90% of the risk of myocardial infarction. This finding occurred in all regions worldwide in both sexes and at all ages.³⁹ The population attributable risk for coronary artery disease due to dyslipidemia was 49.2%, 35.7% due to smoking, 20.1%

secondary to abdominal obesity, 18% as a result of hypertension and 9.9% attributable to diabetes.

Some cardiovascular risk factors such as hypertension, diabetes and dyslipidemia have been found to be more common in SLE patients than in the general population.⁴⁰ In a cross-sectional study of classic cardiovascular risk factors in the John Hopkins Lupus Cohort, 53% of the SLE patients had three or more risk factors for cardiovascular disease with the most prevalent being a sedentary lifestyle (70%), obesity (38%) and hypercholesterolemia (56%).⁴¹ Of note was the finding that the average patients' age in this group was relatively young at 38.3years.

1.5.1 Hypertension

Hypertension is one of the most important preventable causes of premature death worldwide. High blood pressure is defined as a systolic reading equal to or above 140mmHg and/or a diastolic pressure equal to or above 90mmHg. In most countries up to 30% of adults suffer from high blood pressure.⁴² In the INTERHEART study, hypertension accounted for 18% of the population attributable risk for a first myocardial infarction.³⁹ Several pathophysiologic mechanisms link hypertension and coronary heart disease. Hypertension induces endothelial dysfunction and exacerbates the atherosclerotic disease process. A decrease in 'coronary reserve' and increased myocardial oxygen demand occur; both mechanisms contributing to myocardial ischemia.⁴³

Patients with SLE have a higher prevalence of hypertension compared to the general population. In the Toronto Risk Factor Study, 33% of women with SLE had hypertension compared with a prevalence of 13% among the controls.⁴⁴ Increased arterial stiffness in lupus patients is thought to be one of the early vascular changes that leads to major vascular disease including hypertension which results in increased risk for coronary artery disease.⁴⁵ Presence of carotid plaques in lupus patients has been associated with hypertension with an age-adjusted risk of 18% compared to 8% in lupus patients without hypertension.⁴⁶ Hypertension has also been associated with lupus nephropathy and corticosteroid intake.⁴⁷⁻⁴⁹

1.5.2 Dyslipidemia

Epidemiological studies have shown significant correlation between dyslipidemia and the risk of developing acute myocardial infarction.³⁹ Abnormal total cholesterol, triglycerides, LDL and HDL have been associated with atherosclerosis in coronary arteries and the aorta.⁵⁰ Therapeutic reduction in LDL cholesterol has resulted in reduction in the incidence of coronary events.⁵¹

In the John Hopkins lupus cohort, 56% of the patients had hypercholesterolemia.⁴¹ In the Toronto Risk Factor Study, 34% of SLE patients had hypercholesterolemia compared to 36% of the controls.⁴⁴ A study to establish the proportion of dyslipidemia in SLE patients in Indonesia found 43% of the patients to have elevated total cholesterol, 26.4% with abnormal LDL cholesterol, 26% with low HDL levels and 44.2% with hypertriglyceridemia. Overall, 75% of the patients had dyslipidemia. In this sample population, illness period less than 3 years represented a significant correlative factor for dyslipidemia prevalence. Prednisone dose ≥ 30 mg per day was the correlative factor for elevated total cholesterol and hypertriglyceridemia.⁵²

Dyslipidemia in lupus patients tends to occur in two main patterns. Those with active lupus, especially children, usually have hypertriglyceridemia, elevated VLDL and low HDL levels. Patients on corticosteroids and those with secondary anti-phospholipid syndrome have elevated total cholesterol, LDL and triglycerides.⁵³⁻⁵⁵ Factors known to influence dyslipidemia prevalence in SLE include auto-antibodies in lipoprotein metabolism, renal involvement, disease activity and increased lipid level due to prednisone treatment. Hydroxychloroquines decrease lipid levels.^{56,57}

1.5.3 Diabetes

Diabetes is associated with a two- to three-fold increased risk of clinical atherosclerotic disease and the relative impact is substantially greater for women than for men.⁵⁸ Type 2 diabetes is commonly accompanied by other cardiovascular risk factors such as dyslipidemia, hypertension and prothrombotic factors.⁵⁹ Cardiovascular disease is the most common underlying cause of death in diabetics, accounting for 44% of deaths in type 1 and 52% in type 2 diabetes mellitus.⁶⁰ In the Toronto Controlled Lupus Cohort, women with SLE were significantly more likely to have diabetes in comparison with controls (5% versus 1%).⁴⁴

1.5.4 Obesity

Obesity is associated with numerous co-morbidities such as cardiovascular diseases, type 2 diabetes, certain cancers and sleep apnea or sleep-disordered breathing. Obesity is an independent risk factor for cardiovascular disease and is associated with an increase in morbidity, mortality as well as reduced life expectancy. The obese individual has an altered metabolic profile in addition to alterations in cardiac structure and function as adipose tissue accumulates in excess amounts.⁶¹ Abdominal obesity in particular is strongly associated with cardiovascular disease and diabetes even in persons with normal body mass index (BMI).⁶² In the INTERHEART study, abdominal obesity inferred from either the waist: hip ratio or the waist circumference accounted for 20.1% of the population attributable risk for acute myocardial infarction.³⁹ In the John Hopkins lupus cohort, 38% of the patients were obese.⁴¹ In the Toronto Risk Factor Study 15.6% of SLE patients had abnormal waist: hip ratio compared with 9.2% of the controls.⁴⁴

1.5.5 Physical Inactivity

Evidence for an independent role of increased physical activity in the primary prevention of coronary disease has grown in recent years. Sedentary lifestyle is associated with a relative risk of death from coronary heart disease of 1.9 compared with active occupations.⁶³ In the John Hopkins Lupus Cohort, sedentary lifestyle was the most prevalent cardiovascular risk factor, occurring in 70% of the population.⁴¹ Musculoskeletal manifestations of SLE often contribute to reduced physical activity.

1.5.6 Smoking

Smoking is a major modifiable risk factor for atherosclerotic disease, accounting for 35.7% of the population attributable risk for acute myocardial infarction.³⁹ In a study in SLE patients to assess the degree to which cardiovascular risk factors and disease activity were correlated with two year changes in measures of subclinical atherosclerosis, smoking was associated with progression of coronary artery calcium.⁶⁴ Lupus is known to cause accelerated atherosclerosis. Patients who smoke are therefore at substantial risk of developing cardiovascular disease.

1.6 ANTI-INFLAMMATORY THERAPY AND ATHEROGENESIS

Anti-inflammatory therapy utilized in control of lupus may be pro- or anti-atherogenic. Low to moderate dose steroids remain useful in treatment of acute flares in SLE patients and treatment of organ-specific disease especially involving the central nervous system and kidneys. Steroid use is associated with worsening of traditional risk factors for coronary heart disease and an increased risk of coronary disease in patients with SLE. In a cross-sectional study of 264 SLE patients, after adjusting for age, weight and antihypertensive drug use, a 10mg/day increase in prednisone dose led to an increase in serum cholesterol, mean arterial blood pressure and body weight.⁶⁵ The longer the duration and the higher the dose of corticosteroid use, the higher the risk of atherosclerotic disease.^{41, 66} Another study that evaluated the prevalence and correlates of accelerated atherosclerosis in SLE patients found those with carotid plaque to be less likely to have been treated with prednisone.⁶⁷

Unlike corticosteroids, hydroxychloroquine and other anti-malarials may have beneficial effects on lipid profiles and risk of developing diabetes mellitus.⁶⁸ In a retrospective study of the University of Toronto Lupus Clinic database between 1976- 1997, initiation of antimalarials reduced the baseline total cholesterol by 4.1% at 3months while cessation of the antimalarials increased the total cholesterol by 3.6% at 3months .⁶⁹

Methotrexate is used as a disease modifying anti-rheumatic drug (DMARD) in several autoimmune illnesses including SLE. In rheumatoid arthritis patients, use of methotrexate has been shown to decrease cardiovascular mortality,^{70,71} though the inhibition of cyclooxygenase (COX)-2 enzyme by methotrexate promotes atherosclerosis.⁷² Cyclophosphamide use in control of disease activity appears to be beneficial in preventing atherogenesis.⁶⁷ Non-steroidal anti-inflammatory drugs and cyclooxygenase –II inhibitors cause small increments in blood pressure.⁷³

1.7 DISEASE DURATION AND ACTIVITY

In a cross-sectional study of SLE patients who had established cardiovascular disease and those that did not, those with coronary heart disease had a longer mean duration of SLE (12.3 versus 8.1 years).⁴¹ In yet another study that evaluated for cardiovascular disease by carotid

ultrasonography and echocardiography, the presence of atherosclerotic plaques was associated with a longer mean duration of disease and more disease-related damage.⁶⁷ Accelerated atherosclerosis has also been correlated with high disease activity scores.⁶⁶

1.8 UTILITY OF CAROTID ULTRASONOGRAPHY TO DETECT ATHEROSCLEROSIS

Common carotid B-mode ultrasound for detection of atherosclerotic plaques and measurement of carotid intima-media thickness (CIMT) is a non-invasive, sensitive and reproducible technique for identifying and quantifying subclinical vascular disease and evaluating cardiovascular disease risk. Several published prospective studies of CIMT and cardiovascular disease risk have shown that CIMT was significantly associated with risk of myocardial infarction, stroke, coronary heart disease-associated death or a combination of these.⁷⁴⁻⁷⁷ Other methods of detection of atherosclerosis include measurement of the ankle-brachial index, coronary calcium scoring by computed tomography (CT) scan, flow-mediated dilatation and intravascular ultrasound among others. Each modality is associated with some pros and cons that affect its utility. The ankle-brachial index has the challenge of reproducibility while flow-mediated dilatation that measures brachial artery reactivity by ultrasound is yet to be validated and presents difficulties in standardization of its procedural technique in the clinical setting. Coronary calcification detected by electron beam CT scan is an established marker of coronary atherosclerosis but the imaging modality exposes subjects to large amounts of radiation. Furthermore, some advanced atherosclerotic lesions occur without calcification and are undetected by this technique. Intravascular ultrasound on the other hand allows for visualization of atherosclerotic lesions but has key disadvantages of being invasive and costly.⁷⁸⁻⁸⁰ In consideration of the above factors, carotid ultrasonography was the modality chosen for detection of atherosclerosis in this study.

Carotid plaque is defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT greater than 1.5mm that protrudes into the lumen that is distinct from the adjacent boundary.⁸¹ Carotid intima-media thickness greater than or equal to the 75th percentile for the patient's age, sex and race are indicative of increased cardiovascular disease risk and the need for aggressive risk reduction interventions.^{75, 81} No studies have been done to determine normal CIMT values in the African population. Work done in the Netherlands by de Groot et al, established that on average, a

healthy person reaches a CIMT of 0.78mm at the end of 76years and on this basis, a cut-off of 0.8mm has been used to define normal and abnormal CIMT.⁸²

Imaging protocols for CIMT measurements have evolved with time. In the past, ultrasound protocols used in large population based studies assessed CIMT as the mean of the right and left common carotid intima-media thickness. This was shown to result in a reproducibility of less than 0.75.^{83, 84} Recent studies however have indicated a much better or even equal reproducibility (>0.85) in use of the mean maximum CIMT estimates compared to common CIMT. This is derived using images from all the segments; including the common carotid artery, the carotid bulb and the internal carotid artery.⁸⁵

2.0 JUSTIFICATION OF STUDY

Accelerated atherosclerosis and consequent cardiovascular disease is now acknowledged as a primary cause of morbidity and mortality in SLE patients. The risk of developing coronary artery disease in these patients is four- to eight-times higher than that in the normal population. The number of traditional cardiovascular risk factors has been found to be higher in SLE patients than in age- and sex-matched healthy subjects. Prior to this study, no local data existed regarding the burden of atherosclerosis and traditional cardiovascular risk factors in our patients with SLE. We sought to determine the magnitude of atherosclerosis and traditional cardiovascular risk factors in this population with the aim of providing a basis for primary and secondary interventions to reduce cardiovascular morbidity and mortality.

3.0 RESEARCH QUESTION AND OBJECTIVES

3.1 RESEARCH QUESTION

What is the burden of cardiovascular risk in patients with SLE seen at the Kenyatta National Hospital?

3.2 OBJECTIVES

3.2.1 Broad Objective

To determine the prevalence of carotid atherosclerosis and selected cardiovascular risk factors in patients with systemic lupus erythematosus.

3.2.2. Primary objectives

1. To determine the prevalence of hypertension, diabetes, dyslipidemia and obesity in patients with SLE and controls.
2. To determine the prevalence of carotid atherosclerosis as a marker of atherosclerotic disease in SLE patients.
3. To compare prevalence of hypertension, diabetes, dyslipidemia and obesity in SLE patients with that in controls.

3.2.3. Secondary Objectives

1. To document prior cardiovascular events (myocardial infarction, heart failure, angina, stroke, transient ischemic attack) in patients with SLE.
2. To correlate the presence of carotid atherosclerosis and cardiovascular risk factors with the duration of illness, use of corticosteroids and other immunosuppressants.

3. To correlate the occurrence of carotid atherosclerosis with hypertension, diabetes, dyslipidemia and obesity.

4.0 METHODOLOGY

4.1 Study Design

This was a cross-sectional survey in patients with SLE and controls.

4.2 Study Site

The study was carried out at the Kenyatta National Hospital rheumatology clinic, renal clinics and the medical wards.

4.3 Study population

Cases: The study population consisted of all patients with systemic lupus erythematosus attending the Kenyatta National Hospital rheumatology and renal clinics or admitted at the hospital medical wards in the period between January and September 2013. The patients fulfilled the ACR criteria for diagnosis of SLE and were above eighteen years.

Controls: These were individuals without clinical features of SLE employed at the Kenyatta National Hospital or students doing internship or other programs at the hospital. They were sex- and age-matched (to the nearest 5 years) to the SLE patients in the study to facilitate comparison of cardiovascular risk factors in the two groups.

4.4 Inclusion and exclusion criteria

Inclusion criteria for cases

- Above 18 years.
- Confirmed to have SLE (as per the 1997 update of the 1982 ACR revised criteria for the classification of SLE) and giving informed written consent. See Table 1 for ACR criteria.

Inclusion criteria for controls

- Individuals above 18 years who are age-, sex- and race-matched to the cases.

- Persons with no clinical features of SLE who give informed written consent.

Exclusion criteria for cases

- Unwillingness to participate in the study.
- Patients with arthritic necks or other conditions noted on clinical examination that would make it difficult for them to lie flat for carotid ultrasound.
- Recent neck surgery.
- Inability to cooperate due to deranged mental status.

Exclusion criteria for controls

- Not willing to participate in the study.
- Persons known to have SLE.
- Any features on clinical examination or history of symptoms associated with SLE in the present or in the past. These features included:
 - Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, history of pleuritis or pericarditis, history of kidney disease, seizures or psychosis or history of anemia.

4.5 PROCEDURES

CASES

Screening and recruitment

In the period between January and September 2013 the principal investigator identified patients on follow-up for SLE at the Kenyatta National Hospital rheumatology and renal clinics or admitted at the medical wards through their medical records. In the clinics, all files were perused to identify patients on follow-up for SLE. The investigator examined the patients' clinical data to confirm that they fulfilled the 1997 revised ACR criteria for SLE classification. All patients confirmed to have lupus were informed about the purpose of the study and the procedures involved. The patients who accepted to participate signed consent forms and were recruited into the study. The investigator carried out the same procedure in the medical wards on a daily basis to identify and recruit SLE patients admitted at the institution during the study period.

Furthermore, files of patients seen at the rheumatology clinic within the six months prior to study onset (July to December 2012) were retrieved to identify SLE patients who had not returned for follow-up. Such patients were called on phone, informed about the study and given appointments to come participate in study related activities on giving consent.

History taking

Demographic and socio-economic data was sought as per the study questionnaire. Further information regarding the duration of illness, drug history, and history of cardiovascular events was obtained from the patients and from their medical records.

Physical examination

Measurements of height in meters, weight in kilograms, waist and hip circumferences in centimeters and blood pressure in mmHg were taken.

- Height - The patient was asked to remove his/her shoes and cap, if any, and stand straight along a wall where a height scale meter had been placed. Height was then measured in meters and recorded.
- Weight – After removing shoes, heavy clothing such as jackets and items in the pockets, the patient was requested to stand on a weighing scale and the measurement in kilograms recorded. The manufacturer’s instructions on use of the weighing scale was adhered to and calibration done regularly to ensure quality control.
- Waist and hip circumferences – Waist circumference measurement was taken as the circumference midway between the lowest rib and the iliac crest, measured in the horizontal plane. Hip circumference defined as the maximum circumference at the buttocks in the horizontal plane over the greater trochanter was measured and documented.
- Blood pressure – A mercury sphygmomanometer was used to measure blood pressure. The blood pressure was the mean of two readings taken at 5 minute intervals on the right arm with the patient in sitting position after at least 5 minutes of rest, using an appropriate size of a cuff. Appropriate blood pressure bladder cuff size was determined as that with a length at least 80% and a width at least 40% of the upper arm circumference. The Korotkoff phases I and V were documented as the systolic and diastolic pressures respectively.

Laboratory tests

Patients came to the hospital for a fasting lipid profile and fasting blood sugar test on particular days as agreed upon with the principal investigator. Fasting was defined as the patients having taken their last meal (supper), eight or more hours prior to the scheduled appointment. A drop of capillary blood was obtained from a sterilized fingertip area using a sterile needle or lancing device. The drop of blood was placed on a glucose test strip and fasting blood sugar determined using an Accu-Chek glucometer, manufactured by Roche diagnostics, Indianapolis (USA). Two milliliters of blood was then drawn from the antecubital fossa and put into a plain vacutainer bottle for fasting lipid profile test carried out at the department of internal medicine laboratory. The Erba Chem 7 chemistry analyzer machine (Germany) was used to carry out this test. Blood samples were assayed using commercially available kits manufactured by Human Diagnostics Worldwide (Germany). The manufacturer's instructions for the specific test kits were adhered to. Internal quality control tests were carried each day the tests were done. The chemistry analyzer machine was calibrated by the Kenya Bureau of Standards and further external quality control was carried out regularly by the Human Quality Assessment Services.

Carotid Ultrasonography

Carotid ultrasonography was done on same day the patient came for laboratory tests. The ultrasonography was carried out at the department of diagnostic imaging and radiation medicine, University of Nairobi by a consultant radiologist who is experienced in vascular ultrasound, assisted by a team of other consultant radiologists.

The patient was placed supine on the examination couch with the head slightly extended and the neck rotated in the direction opposite to the probe. The carotid arteries were assessed by B-mode ultrasound using a linear-array transducer operating at a fundamental frequency of at least 7 MHz. The spectral angle of interrogation was maintained at 45 – 60°. Gray-scale examination began in transverse projection and later in the longitudinal plane. Scans were obtained along the entire course of the cervical carotid artery from the supraclavicular notch, cephalad to the angle of the mandible. The layers of the carotid arteries were examined in longitudinal view to measure the intima-media thickness. Normally, the carotid wall demonstrates two nearly parallel echogenic lines separated by a hypoechoic to anechoic region. The first echogenic line bordering

the vessel lumen represents the lumen-intima interface and the media is the anechoic/hypoechoic zone between the echogenic lines. The distance between the echogenic lines represents the combined thickness of the intima and media (intima-media thickness).⁸⁶ The mean maximum CIMT was derived using images from all the carotid artery segments bilaterally; including the common carotid artery, the carotid bulb and the internal carotid artery. 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 1.5mm that protruded into the lumen that was distinct from the adjacent boundary.

To ascertain the reliability of the observers in measuring the mean CIMT and identifying carotid plaques, every fifth patient was evaluated separately by two radiologists to assess for inter-observer variability. Furthermore, five different radiologists repeated ultrasonographic assessment they had done on particular patients at earlier dates and the findings were used to determine the intra-observer variability. The role of chance in inter-observer and intra-observer agreement was determined using kappa statistic during analysis.

CONTROLS

The controls were age-, sex-and race- matched staff and students (doing internship or other programs) at the Kenyatta National Hospital. The principal investigator personally and through departmental heads, disseminated information regarding the study purpose and procedures to staff and students in the various hospital sections. Those who were willing to participate and who matched the cases were screened for symptoms or clinical features of SLE. Those without features of SLE who signed consent forms were enrolled into the study. Blood pressure and anthropometric measurements (weight, height, waist and hip circumference) were taken. A date for laboratory testing was agreed upon with each control, when the subject would come to work fasted for at least eight hours and undergo fasting blood sugar and fasting lipid profile tests as stated for the cases.

4.6 Definition of Study Variables

Carotid Atherosclerosis

Abnormal carotid intima-media thickness (CIMT) and/or the presence of carotid plaque as established on carotid ultrasonography.

- **Abnormal CIMT** - A value greater than 0.8mm measured during carotid ultrasound as described in the procedures section above.
- **Carotid plaque** - The presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT greater than 1.5mm that protrudes into the lumen that is distinct from the adjacent boundary.

Hypertensive status

Mean systolic blood pressure ≥ 140 mmHg and/or a mean diastolic BP ≥ 90 mmHg (JNC VII classification – appendix 5) or being on antihypertensive medication.

Diabetes

Fasting blood sugar ≥ 7.0 mmol/L (WHO criteria – appendix 5) or being on diabetic medication i.e. insulin or oral hypoglycemic agents.

Obesity

Obesity was defined as per WHO guidelines indicated in appendix 6.

BMI ≥ 30 [BMI = Weight (kilograms) / Height² (meters)] or

Waist circumference (WC): In females > 80 cm and in males >94 cm or

Waist: Hip ratio: In females ≥ 0.85 and in males ≥ 0.90

Dyslipidemia

Abnormality in any of the lipid fractions as classified in the NCEP/ATP III classification (see appendix 4).

Cardiovascular events

Patients were classified as having had cardiovascular events if there was history and documentation of any of the following: Myocardial infarction, Angina, Stroke or Transient ischemic attack (TIA), prior angioplasty or coronary artery bypass grafting (CABG).

4.7 Data Management and Analysis

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 plaques) and cardiovascular risk factors were analyzed and presented as proportions. Anthropometric measurements were classified as per 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 chi-square test or Fisher's exact test where appropriate. Comparison of anthropometric measurements between the two groups was done using Student's t test. Odds ratios were calculated to estimate the risk among the SLE patients as compared to the controls. All statistical tests were performed at 5% level of significance (95% confidence interval).

5.0 Ethical Considerations

Ethical approval was granted by the Kenyatta National Hospital/University of Nairobi ethics committee before data collection commenced. Informed consent was sought from study participants who accepted to be involved in the study voluntarily and right to withdraw consent was upheld. Blood pressure measurement, carrying out of laboratory tests and carotid ultrasound was done at no cost to the subjects. The patients (cases) had their blood pressure recorded in their files and a copy of laboratory and carotid ultrasound results placed in the files. Attending clinician(s) were informed of any abnormal results so as to institute treatment or other measures to prevent cardiovascular disease. Controls with abnormal results were also informed and referred to appropriate clinics within the hospital. Patients found to have carotid atherosclerosis were considered to be at high risk of cardiovascular disease (e.g. stroke and myocardial infarction). In these cases the investigator informed the clinicians so that measures to reduce this risk were put in place. The recommended measures included better control of SLE disease activity using immunosuppressants, strict control of lipid levels, sugar and blood pressure control where applicable and weight loss programs for the obese.

6.0 RESULTS

This study was carried out in the period between January and September 2013. At the end of the study period, 66 patients and 66 healthy controls had participated in the study and had complete data. Among the SLE patients, 56 were recruited from the rheumatology clinic, 6 from the renal clinics and 5 from the medical wards. The recruitment of SLE patients and controls was done as indicated in the flow-chart below.

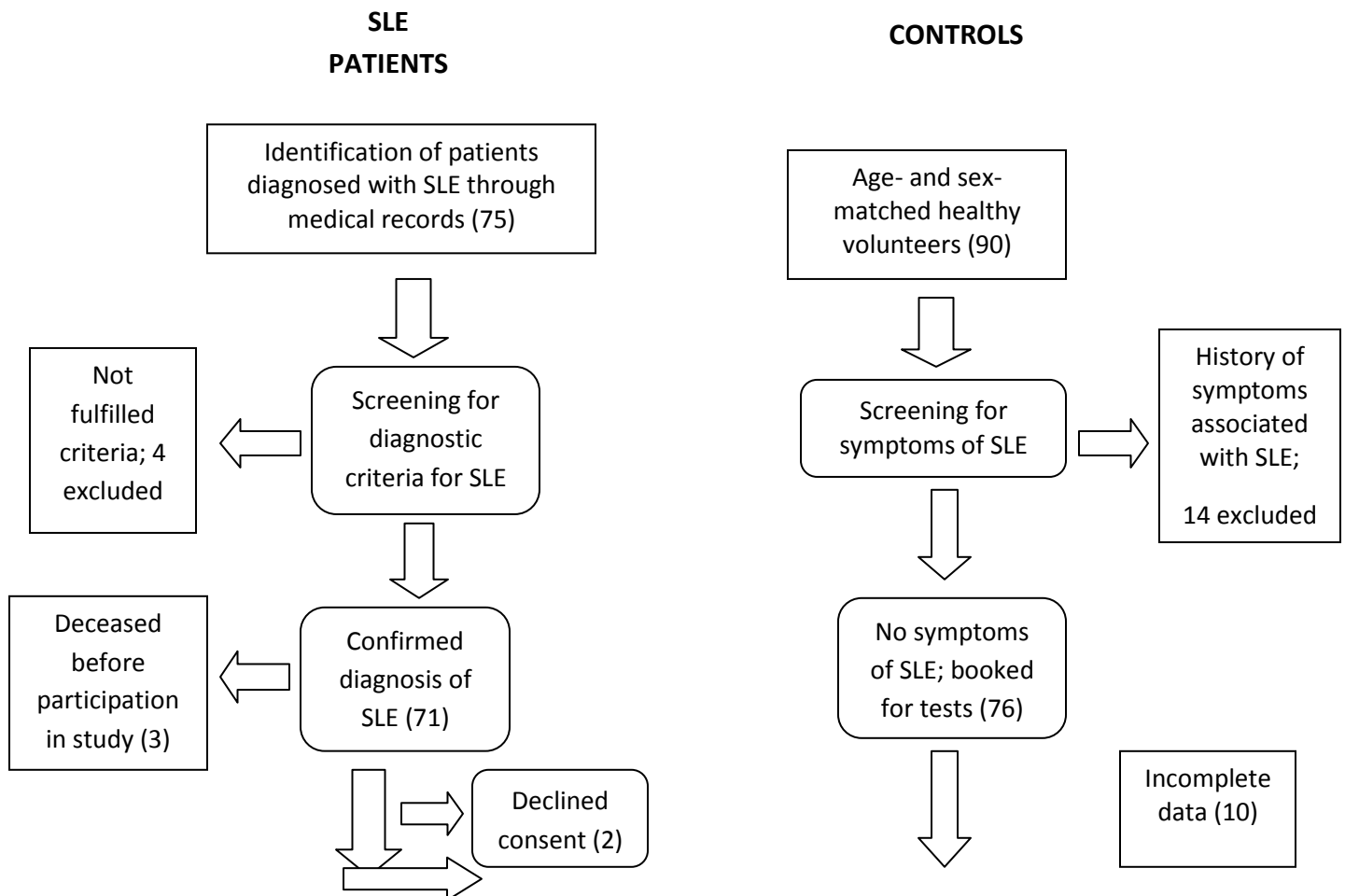




Figure 1: Recruitment flow chart for SLE patients and controls

Table2: Baseline characteristics of SLE patients and controls

VARIABLE	SLE PATIENTS n=66	CONTROLS n=66	P-VALUE
Age- years Mean (SD)	35.9 (10.9)	35.7 (10.2)	0.908
Sex Female-No. (%)	63 (95.5%)	63 (95.5%)	1.000
Female: Male ratio	21:1	21:1	
Duration since SLE diagnosis			
Median (IQR)	2 years (1-4)	N/A	N/A
Range	1month – 13years		
Age at diagnosis of SLE			
Mean (SD)	33.1 years (10.5)	N/A	N/A
Range	16 – 56 years		

The table shows that this was a young population with a mean age of 35.9 years (10.9 years SD) in the SLE patients and 35.7 years (10.2 years SD) in the controls. Majority of the lupus patients (95.5%) were female and the female to male ratio was 21:1 in the patients and controls. Mean BMI in SLE patients was 23.0 compared to 26.1 in controls (p=0.001). The mean systolic blood pressure was 124.3mmHg in patients and 121mmHg in controls (p= 0.295) while mean diastolic blood pressure was 80.9mmHg in SLE patients and 80.3mmHg in the controls (p= 0.700).

Table 3: Anti-inflammatory drugs, statins and anti-platelet agents used by SLE patients

VARIABLE	FREQUENCY (%) n=66
Corticosteroids – Prednisone	58 (87.9)
Dosage (n=58)	
Low dose; <10mg/day	20 (34.5)
Medium dose; 10 – 20mg/day	32 (55.2)
High dose; >20mg/day	6 (10.3)
Hydroxychloroquine	51 (77.3)
Methotrexate	14 (21.2)
Azathioprine	13 (19.7)
Mycophenolate Mofetil	6 (9.1)
Rituximab	1 (1.5)
Methotrexate/ Azathioprine/ Mycophenolate Mofetil/ or a combination	31 (47)
NSAIDs (regularly)	7 (10.6)
Statins	1 (1.5)
Anti-platelet agents	4 (6.1)

Table 3 shows that majority of the patients (87.9%), took steroids regularly as part of their treatment. Of these, most (55.2%) were on a prednisone dosage of 10 – 20milligrams per day.

Three quarters of the patients were on the hydroxychloroquine and nearly half of them 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).

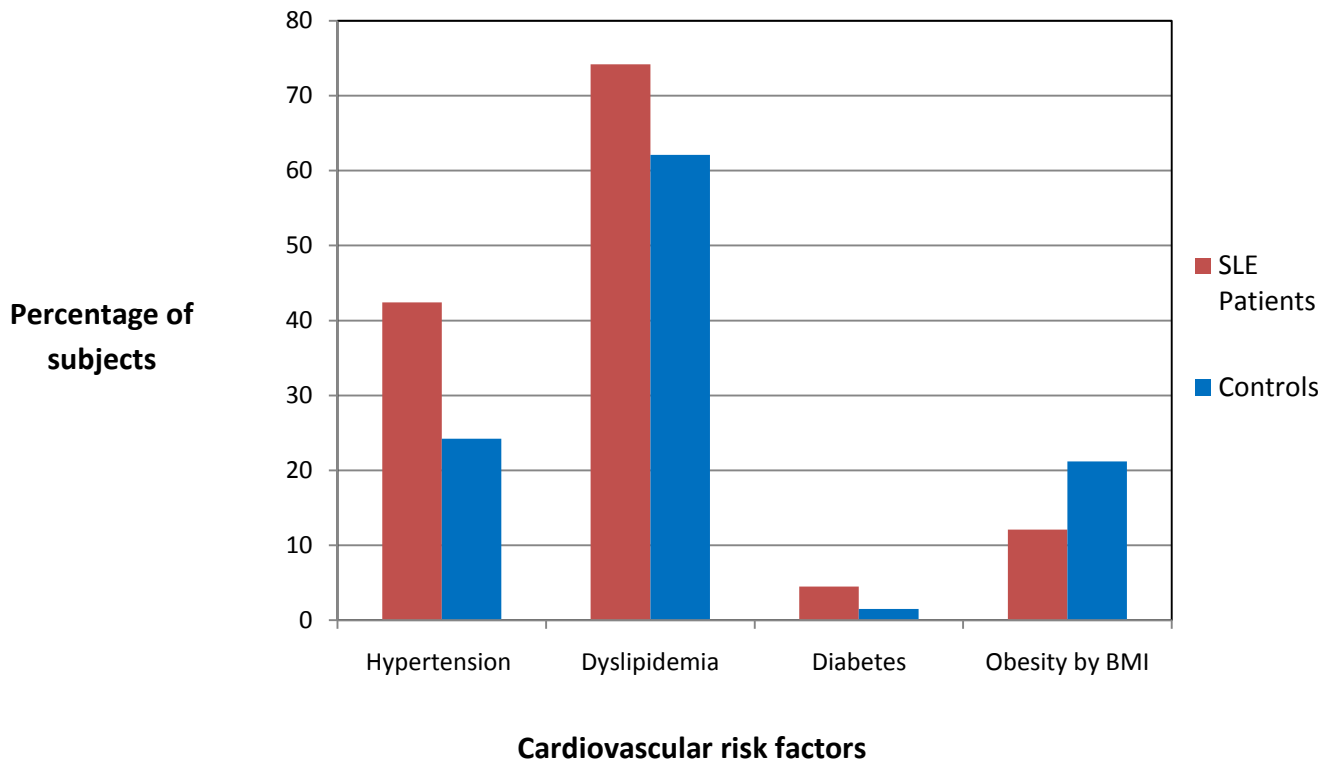


Fig 2: Prevalence of cardiovascular risk factors in SLE patients and controls

Hypertension was more common among the patients than controls, at 42.4% and 24.2% respectively. Dyslipidemia occurred in majority of the patients (74.2%) and controls (62.1%).

Three patients (4.5%) and one control (1.5%) had diabetes. Among the SLE patients, 12.1% had obesity as per the WHO BMI classification compared with 21.2% of the controls.

Table 4: Comparative analysis of prevalence of cardiovascular risk factors in SLE patients and controls

VARIABLE	SLE		OR (95% CI)	P-value
	PATIENTS n=66 (%)	CONTROLS n=66 (%)		
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 \geq 30	8 (12.1)	14 (21.2)	0.6 (0.2 – 1.7)	0.330
Obesity by W:H ratio Females \geq0.85 Males \geq0.90	22 (33.3)	16 (24.2)	1.6 (0.7 – 3.3)	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 4 shows the result of comparative analysis of the prevalence of the cardiovascular risk factors in the SLE patients and healthy controls. Hypertension was more common among the patients than controls and this was statistically significant (p=0.027). Dyslipidemia occurred in majority of the patients and the controls. Twenty two lupus patients (33.3%) and 23 controls (34.8%) had hypercholesterolemia (p=0.854), low HDL levels occurred in 50% of the patients and 34.8% of the controls (p=0.078), high LDL levels were found in 20 patients and 20 controls while hypertriglyceridemia occurred in 36.4% of patients and 27.3% of controls (p=0.350).

There was no statistically significant difference in the occurrence of obesity as per the WHO BMI classification in lupus patients compared to controls. Abdominal obesity as assessed by the waist to hip ratio was more frequent among the patients than the controls but this difference was not significant ($p= 0.249$). Of note, 18.2% of the SLE patients were underweight ($BMI < 18.5$).

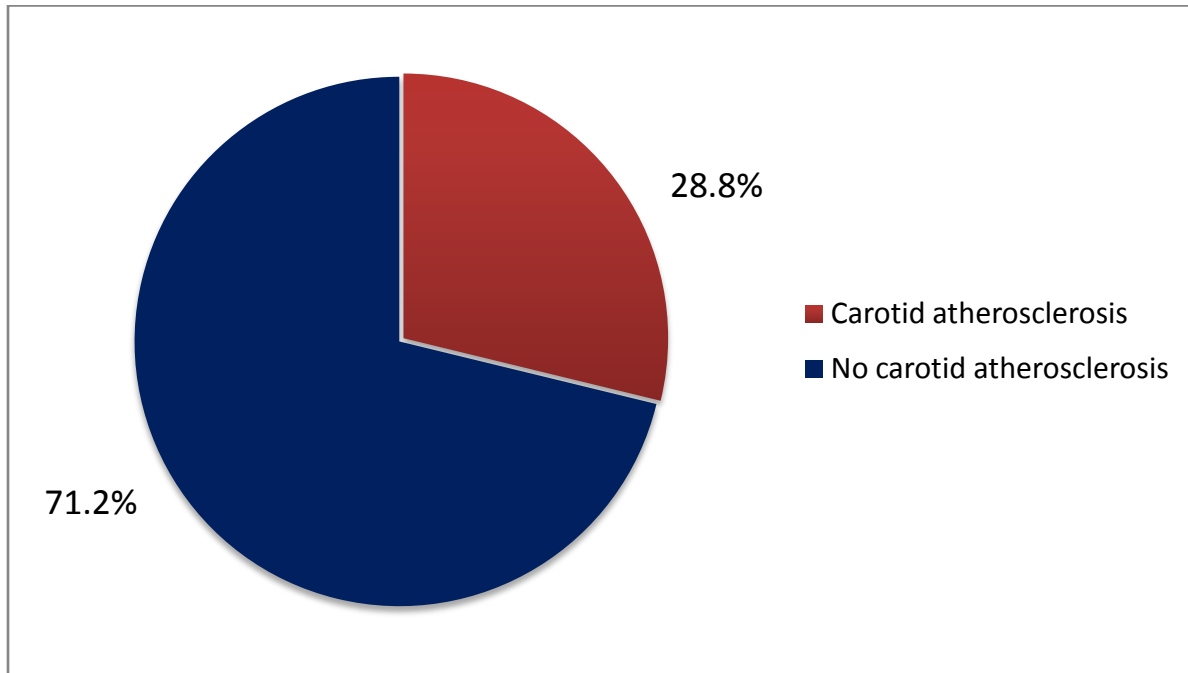


Fig 3: Prevalence of carotid atherosclerosis in SLE patients

Carotid atherosclerosis occurred in 19 (28.8%) of the 66 lupus patients. Nine patients (13.6%) had abnormal CIMT while carotid plaque(s) was observed in 15 patients (22.7%). 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 5: Correlation of carotid atherosclerosis and cardiovascular risk factors with duration of illness in SLE patients

VARIABLE	DURATION OF ILLNESS Median in years (IQR)	P-value
Carotid atherosclerosis	4.0 (2.0-6.0)	0.040
Abnormal CIMT	5.0 (4.0-7.5)	0.006
Carotid plaque(s)	2.0 (1.5-5.0)	0.561
Hypertension	2.0 (2.0-3.0)	0.963
Dyslipidemia	2.0 (1.0-3.0)	0.135
Diabetes	1.5 (1.0-3.0)	0.408
Obesity by BMI (BMI \geq30)	4.0 (3.0-5.0)	0.021
Obesity by Waist to Hip Ratio	3.0 (2.0-5.0)	0.166
Obesity by Waist Circumference	3.0 (2.0-5.0)	0.166

Lupus patients with carotid atherosclerosis and obesity (by BMI assessment) had significantly longer duration of illness compared to those without these findings (p-values = 0.040 and 0.021 respectively) as indicated in Table 5 above. Analysis to assess for correlation between carotid atherosclerosis and the use of corticosteroids or other immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil or a combination of these) 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.

Twelve of the 66 lupus patients had their carotid ultrasonography done by two consultant radiologists separately. An assessment of variability in the detection of carotid plaque and measurement of the CIMT was done using the kappa statistic and Pearson correlation coefficient respectively. The results of the analysis showed acceptable agreement in the findings by the different observers [kappa value= 1.0 (p=0.001) in detection of carotid plaque and Pearson correlation coefficient of 0.98 (p=0.004) in CIMT measurement]. Another five patients had their carotid ultrasonography repeated by the same consultant radiologist who had carried it out at an earlier date and the variability analysis done. This intra-observer variability analysis involved five different observers and the results found acceptable reproducibility of the findings [kappa value= 1.0 (p=0.025) in plaque detection and Pearson correlation coefficient =0.97 (p=0.001) in CIMT measurement].

7.0 DISCUSSION

This study population consisted predominantly of young females in the reproductive age group with a relatively short median duration of SLE (2years since diagnosis). The mean age at diagnosis of lupus was 33.1years 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 Nigeria¹¹ and mean age of 33years at diagnosis in a South African study with a female to male ratio of 18:1.¹² In Tunisia a retrospective study to describe the epidemiological and clinical profile of the disease found a female to male ratio of 11:1.⁸⁷

Hypertension accounted for a population attributable risk for a first myocardial infarction of 18% in the INTERHEART study.³⁹ Our study found hypertension to occur in 42.4% of the lupus patients and 24.2% of the controls and the difference in prevalence of hypertension in the two groups was 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.⁴⁵ Other factors that have been associated with hypertension in these patients include lupus nephropathy and steroid intake.⁴⁷⁻⁴⁹ In our study we neither assessed for level of inflammation nor evaluated for lupus nephropathy and thus could not pursue such correlations. We note however that up to 87.9% (58 out of 66) of our SLE patients used corticosteroids on a regular basis. Probably due to the fact that almost all our patients were on steroids we did not establish correlation 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 controls⁴⁴ while 41% in the John Hopkins Lupus cohort were hypertensive.⁴¹

Dyslipidemia occurred in three quarters of our SLE patients (74.2%) compared to 62.1% of the controls ($p=0.135$). A third of our lupus patients (33.3%) had hypercholesterolemia, half had low HDL levels, 30.3% had elevated LDL and 36.4% had hypertriglyceridemia. Only one patient in our study was on a statin, indicating that dyslipidemia in this group was largely untreated. Our findings were similar to those in a study that evaluated the proportions of dyslipidemia in SLE patients in Indonesia.⁵² 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 the study were on corticosteroids and lupus duration less than three years correlated with dyslipidemia prevalence. Furthermore, prednisone dose ≥ 30 mg per day was associated with hypercholesterolemia and hypertriglyceridemia. No association between steroid use and dyslipidemia was demonstrated in our SLE patients, majority of whom used the corticosteroids regularly. We also observed that a big proportion (62.1%) of our controls who were staff or students at the Kenyatta national hospital had dyslipidemia. An earlier study by Kirui et al⁸⁸ 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 our 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 20milligrams 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 diabetic⁴⁴ comparable to 7% in the John Hopkins Lupus cohort.⁴¹

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^{39, 62} occurred almost similarly in our 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.^{41,44} Variation in obesity prevalence in these studies is partly due to use of different cut-offs to define obesity.

In this generally young population, we found the prevalence of carotid atherosclerosis to be 28.8%. Carotid plaque(s) occurred in 22.7% of the patients and abnormal CIMT in 13.6%. In a study that assessed the prevalence and correlates of accelerated atherosclerosis in SLE patients in New York, Roman et al⁶⁷ found a higher prevalence of carotid plaque, occurring in 37.1% of the patients. Mean age of patients in that study was 44years with a mean duration of illness of 10.75years. The prevalence of hypertension in that study was 28.9% compared to 42.4% in our patients while occurrence of diabetes in the both studies was fairly similar. Our population was also younger (mean age of 33.1years) and had a median duration of SLE of only 2years. We however noted that majority of patients reported to have experienced the symptoms of SLE for variable periods of time (up to 3 years in some cases) before diagnosis had been made. Another study in British women with SLE that sought to evaluate the health-related quality of life, smoking and atherosclerosis in the lupus patients 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 47.6years and mean duration of illness 11.4years. Amongst the British SLE patients, 30% were hypertensive and 12% had hypercholesterolemia.⁸⁹ Our population therefore had lower rates of carotid plaque and abnormal CIMT than those in the aforementioned studies despite having higher rates of hypertension and hypercholesterolemia. This was probably a consequence of our lupus patients being younger and having had the disease for shorter duration compared to those in the other two studies. Another possible explanation of this discrepancy would be the observation in past studies that traditional cardiovascular risk factors do not fully explain accelerated atherosclerosis in lupus patients but that other factors such as the inflammatory process in these patients play an important role.^{36,90}

In our SLE patients, carotid atherosclerosis was associated with a longer duration of illness, a finding that was also observed in the study by Roman et al⁶⁷ and in a more recent study that assessed the progression of carotid atherosclerosis in SLE patients.⁹¹ 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. Owing to our smaller study population we did not carry out multivariate analysis to assess for such independent association.

In this study we evaluated patients' clinical records and took history to assess for prior cardiovascular events. Of the 66 patients, 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. Ultimately a total of six patients (9.1%) had a prior cardiovascular event. Four of these patients were on aspirin. The benefits of low-dose aspirin in secondary prevention of cardiovascular disease has been established in the general population^{92, 93} and use for primary and secondary prevention in high risk lupus patients has been proposed.⁹⁴ The occurrence of cardiovascular events in this population with a relatively short duration of SLE affirms the need to pay attention to their cardiovascular risk.

8.0 CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

8.1 CONCLUSION

A significant proportion of SLE patients were found to have atherosclerosis. Hypertension was more common in these patients than the controls. There was no significant difference in the occurrence of diabetes, dyslipidemia and obesity in the SLE patients and controls.

8.2 RECOMMENDATIONS

1. Cardiovascular risk assessment and stratification should be done in SLE patients and appropriate strategies put in place to prevent cardiovascular disease.
2. Similar studies should be carried out on a larger population to provide more information on atherosclerosis in SLE patients in this country.

8.3 STUDY LIMITATIONS

Due to financial constraints, comparison of atherosclerosis in SLE patients and controls was not done. We acknowledge that doing so would have given more information on cardiovascular risk in patients with lupus.

9.0 APPENDIX

APPENDIX 1: REFERENCES

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APPENDIX 2: STUDY PRO-FORMA DOCUMENT/QUESTIONNAIRE

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

No.....

Date.....

A. Demographic Data

1. Age.....

Sex.....

1=Female; 2=Male

2. Marital status.....

1 = Married

2 = Single

3 = Widowed

4 = Divorced

3. Level of formal education.....

1 = Tertiary

2 = Primary

3 = Secondary

4 = College

5 = None

4. Current status of employment.....

1 = Unemployed

2 = Employed

3 = Self-employed

4 = Retired

B. Duration of illness

1. Age at diagnosis of SLE.....

2. Duration of SLE (time since diagnosis)
 Months.....

Years.....

C. Symptoms, Signs and Investigation results prior to diagnosis of SLE

Criterion	Tick if present
Malar rash Fixed erythema, flat or raised	
Discoid rash Erythematous raised patches	
Photosensitivity Skin rash as unusual reaction to light	
Oral ulcers Oral or nasopharyngeal ulceration	
Non-erosive arthritis Involving 2 or more joints	
Pleuritis or pericarditis Pleuritis – pleuritic pain, pleuritic rub, pleural effusion Pericarditis – pericardial rub, pericardial effusion, or on ECG	
Renal disorder Persistent proteinuria >0.5g/day or >3+ OR cellular casts	
Neurologic disorder Seizures or psychosis in absence of offending drugs or metabolic derangements	
Hematologic disorders Hemolytic anemia with reticulocytosis Leucopenia <4000/mm ³ on 2 or more occasions Lymphopenia <1500/mm ³ on 2 or more occasions Thrombocytopenia <100,000/mm ³ in absence of offending drugs	
Immunologic disorders Anti-DNA, Anti Smith, +ve Antiphospholipid antibodies	
Positive Antinuclear Antibody	

Total No. of criteria present =

D. Treatment and Medical History

1. Treatment received

Treatment	Yes/No	Regular	Intermittent	Symptomatic	No recall
Corticosteroids -LD (Prednisone <10mg/day) -MD (Prednisone 10-20mg/day) -HD (Prednisone >20mg/day)					
Antimalarials -Hydroxychloroquine					
Immunosuppressants -Cyclophosphamide -Methotrexate -Azathioprine -Mycophenolate					
Immunomodulators -Belimumab -Rituximab					
NSAIDS -Ibuprofen -Diclofenac -Naproxen or others					

2. Are you currently on treatment for any of these illnesses? (Yes/No)

Hypertension

Diabetes OHA's..... Insulin

Renal failure On Dialysis (Yes/No).....

Kidney transplant(Yes/No).....

Heart failure

3. Are you on any of these medications? (Yes/No)

Statins

Antiplatelet drugs.....

Nitrates

4. Do you have history of any of the following illnesses/events? Yes/No (To include any file documentation).

Heart failure

Stroke or Transient ischemic attack.....

Myocardial infarction

Angina.....

History of coronary angiography.....

E. Physical Examination

1. Blood pressure (in mmHg)

1 st Reading.....	2 nd Reading.....	Mean
BP.....		

2. Waist Circumference (in centimeters)

.....

3. Hip circumference(in centimeters)

.....

3Waist to Hip Ratio

.....

APPENDIX 3: Laboratory and carotid ultrasound results form

Case No. Control No.....

1. Fasting Blood Sugar

Diabetic (YES/NO)

3. Fasting Lipid Profile

- a) Total cholesterol.....1 = Elevated, 2 = Normal, 3 = Low
- b) HDL cholesterol.....1 = Elevated, 2 = Normal, 3 = Low
- c) LDL cholesterol1 = Elevated, 2 = Normal, 3 = Low
- d) VLDL cholesterol.....1 = Elevated, 2 = Normal, 3 = Low

4. Carotid Ultrasound

CIMT reading.....

CIMT Abnormal.....(Yes/No)

Carotid Plaque(Present/ Absent)

APPENDIX 4: NCEP/ATP III Guidelines for diagnosis of dyslipidemia

Dyslipidemia will be classified as per National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) guideline shown below:

1. Total cholesterol	<5.17mmol/l	- Desirable
	5.17 – 6.18mmol/l	- Borderline high
	>6.21mmol/l	- High
2. LDL cholesterol	<2.58mmol/l	- Optimal
	2.58 – 3.33mmol/l	-Near optimal
	3.36 – 4.11mmol/l	-Borderline high
	4.13 – 4.88mmol/l	-High
	>4.91	-Very high
3. HDL cholesterol	<1.03mmol/l	-Risk indicator
	<1.29mmol/l	-Standard risk level
	>1.55mmol/l	-Favourable
4. Triglycerides	<1.69mmol/l	-Normal
	1.69 – 2.25mmol/l	-Borderline high
	2.26 – 5.64mmol/l	-High
	>5.65mmol/l	-Very high

APPENDIX 5: Guidelines for diagnosis of hypertension and diabetes

1. Diagnosis of Hypertension

Blood pressure readings will be categorized as per the following guidelines:

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7):

CATEGORY	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)
Normal	<120	and	<80
Pre-hypertension	120 – 139	or	80 – 89
Hypertension Stage 1	140 – 159	or	90 – 99
Hypertension Stage 2	≥ 160	or	≥ 100

2. Diagnosis of Diabetes

Diabetes will be diagnosed as per the WHO guidelines for definition and diagnosis of diabetes mellitus and intermediate hyperglycemia indicated below:

CATEGORY	Plasma Glucose Levels
Diabetes Mellitus	Fasting Blood Sugar ≥ 7.0 mmol/l OR Random Blood Sugar ≥ 11.1 mmol/l
Impaired Glucose Tolerance	Fasting Blood Sugar 6.1 – 6.9 mmol/l

APPENDIX 6: WHO Guidelines on Obesity

The WHO International Classification of Adult underweight, overweight and obesity.

Classification	BMI (kg/m ²) Principal cut-off points
Underweight	<18.50
Severe thinness	<16.00
Moderate thinness	16.00 – 16.99
Mild thinness	17.00 – 18.49
Normal range	18.50 – 24.99
Overweight	≥25.00
Pre-obese	25.00 – 29.99
Obese	≥30.00
Obese Class I	30.00 – 34.99
Obese Class II	35.00 – 39.99
Obese Class III	≥40.00

The WHO Classification of Abdominal Obesity

Variable	Values
Waist circumference	Males > 94cm Females > 80cm
Waist to Hip ratio	Males ≥ 0.90 Females ≥ 0.85

APPENDIX 7: CONSENT EXPLANATION FORM

Title of Study: Cardiovascular risk factors and carotid atherosclerosis in patients with systemic lupus erythematosus at Kenyatta National Hospital.

Principal Investigator: Dr Betty Shiruli

Introduction: I, Dr Betty Shiruli, of the department of clinical medicine and therapeutics, University of Nairobi, am conducting a study under the above title. In this study we want to know how many of our lupus patients have hypertension, diabetes, obesity, high cholesterol levels and thickened body arteries (atherosclerosis). Persons without this disease will also be included in the study to compare with those with lupus.

Procedures to be followed: Upon accepting to participate in this study, you will be asked to sign an informed consent form. After this, we will ask you questions regarding your present illness, past illness, drugs you have used and the duration you have been unwell. We will also be interested in knowing your age, marital status and level of education. We will then measure your blood pressure, weight, height, waist circumference and hip circumference. We will require you to return on a date we shall agree on together when we will carry out blood tests and ultrasound of your neck arteries. Transport cost for the second visit will be reimbursed to you according to the current public transport cost from your home to Kenyatta National Hospital. On this day you will need to come while fasted (not taken breakfast), and we will take some blood (2milliliters) to test for your blood glucose and cholesterol levels. In addition, we will carry out ultrasound of your neck arteries to check for changes in the artery walls. This test is painless and harmless.

Benefits: The measurements, blood tests and ultrasound will be done at no cost to you. A copy of each test result will be placed in your clinic file and will be used by your doctor to put in place measures to reduce the risk of stroke or heart attack in you. Persons without lupus involved in this study will be given a copy of their results and referred to an appropriate clinic if they are found to have abnormal test results.

Injury/Risk: You will encounter no risk while we measure your blood pressure, weight, height, hip and waist circumferences. You will have slight discomfort from the needle pricks when we

will be taking blood to measure your sugar and cholesterol levels. There shall be no risk to you while you undergo the neck ultrasound.

Duration of participation: In the first encounter, we will require 30minutes to ask you a few questions and measure your blood pressure, weight, height, waist and hip circumferences. During your second visit we will require an hour to get the blood samples and to carry out the neck ultrasound.

Who can participate in this study?: Any person aged 18years and above, confirmed to have lupus and willing to sign an informed consent form. In addition persons without lupus aged 18years and above will be included in the study for the purpose of comparison. This group will have similar measurements and blood tests done but will not undergo ultrasound.

Assurance of confidentiality of volunteer's identity: Records relating to your participation in this study will remain confidential. Your name will not be used in any report resulting from this study. All computerized and laboratory specimens will contain only a unique study number.

Researcher's contacts: If during the course of the study you have any questions concerning the nature of the research, you can contact:

Dr Betty Shiruli P.O. BOX 19676 – 00202, Nairobi, Kenya. Telephone Number: 0721-803958

If you will have questions that would like addressed by persons not involved in this research, you may contact:

The Chairman or Secretary

Kenyatta National Hospital/University of Nairobi Ethics Research Committee

Telephone Number: 020-0726300 Extension 44102

CONSENT FORM

I, do freely give permission to participate in the intended research study. I acknowledge that I have understood the contents of this form. The

procedures involved have been explained to me by
in a language that I understand well. I have agreed to have the examination and tests carried out
on me. I understand that my participation is voluntary and that I may revoke my consent and
withdraw from the study without any prejudice.

Volunteer name

Signature..... Date.....

Name of Investigator.....

Signature..... Date

APPENDIX 8 : KISWAHILI VERSION OF CONSENT EXPLANATION FORM

MAELEZO YA FOMU YA MAKUBALIANO

Mada: Cardiovascular risk factors and carotid arteriosclerosis in patients with systemic lupus erythematosus at Kenyatta National Hospital.

Mchunguzi mkuu: Dkt. Betty Shiruli wa Idara ya Matibabu katika Chuo kikuu cha Nairobi

Maelezo: Katika uchunguzi huu, tuna haja ya kujua idadi ya watu wenye magongwa ya mafuta kwa mishipa ya damu, sukari, presha ya damu, kuzidi uzani, na kiwango cha mafuta mwilini. Tutalinganisha vipimo hivi katika watu walio na ugonjwa wa Lupus na wale wasio na ugonjwa huu.

Mpangilio: Baada ya kusoma maelezo na kukubali kushiriki katika uchunguzi huu, utahitajika kutia sahihi katika fomu ya kukubali kushiriki. Utatueleza kuhusu umri wako, ndoa, masomo, ugonjwa wako wa sasa au awali na madawa unayo tumia. Baada ya hayo tutapima presha ya damu, uzani wako, kipimo cha kiuno na paja. Tutakubaliana nawe kuhusu siku ya kurudi kupimwa damu na picha. Tutagharamia malipo ya nauli ya kurudi hospitalini mara ya pili kulingana na viwango vya usafiri wa uma. Siku hiyo utakuja kama haujala chakula cha asubuhi, tutatoa damu (mililita 2) ya kupima sukari, na kiwango ya mafuta mwilini. Kisha tutapiga picha shesheli yakuchugua mishipa ya damu ya shingo. Picha hii haina madhara yoyote kwako.

Faida kwa muhisika: Vipimo vyote vitafanywa bila malipo kutoka kwako. Matokeo ya vipimo yatewekwa kwa faili yako ya matibabu na yatatumiwa na daktari wako kukushauri na kupunguza uwezekano wa ugonjwa wa moyo au ubongo.

Madhara : Hakuna madhara inatarajiwa katika vipimo vya presha, uzani, kiuno na paja au picha shesheli ya shingo. Utahisi maumivu kidogo kutoka kwa shindano ya kutoa damu lakini haitadumu kwa mda mrefu .

Muuda wa kushiriki: Siku ya kwanza, tutahitaji nusu saa kukuuliza maswali machache na kufanya vipimo. Tunapokutana mara ya pili tutahitaji muda wa saa moja kukamilisha vipimo vya damu na picha.

Nani anaweza kushiriki katika uchunguzi?: Mtu yeyote aliye na miaka 18 au zaidi na amepatikana na ugonjwa wa lupus na yuko tayari kutoa hiyari. Watu wasio na ugonjwa wa lupus walio na miaka 18 au zaidi na wako tayari kutoa hiyari watahirikishwa kwasababu ya kulinganisha. Hawa watafanyiwa vipimo zote bila picha pekee yake.

Hakikisho la siri ya muhusika: Maelezo na matokeo ya vipimo vyako yatatumiwa kwa uchunguzi pekee. Jina lako halitatumiwa kwenye rekodi au mahabara bali tutambua kila mshiriki kwa nambari maalum.

Anwani ya mchunguzi: Ukiwa na swali lolote kuhusu uchunguzi unaweza kuwasiliana na:

Dkt Betty Shiruli. S.L.P 19676-00202 Nairobi, Kenya. Nambari ya simu: 0721-803958

Kama una swali ungependa kumuuliza mtu asiyehusika moja kwa moja katika uchunguzi huu wasiliana na;

Mwenyeketi au Katibu,

Kenyatta National Hospital/ University of Nairobi Ethics Research Committee

Nambari ya simu 020-0726300, Ext 44012

FOMU YA MAKUBALIANO

Mimi natoa ruhusa ya kushiriki katika uchunguzi huu. Nimefahamishwa na kuelewa maelezo ya fomu hii. Nimeelezewa vipimo vitakavyofanywa nakatika lugha ninayofahamu na ninakubali vipimo hivyo. Ninafahamu pia ya kwamba kushiriki katika uchunguzi ni kwa hiyari na ninaweza kujiondoa bila kuadhiriwa.

Jina la muhusika.....

Sahihi..... Tarehe.....

Jina la mchunguzi.....

Sahihi.....