HIGH PREVALENCE OF METABOLIC SYNDROME IN PATIENTS WITH SLE IN THE WESTERN CAPE

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DECLARATION

I, NA Nkabane, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

INTRODUCTION: Patients with systemic lupus erythematosus (SLE) are at increased risk of the metabolic syndrome (MetS) and its complications. In the absence of published studies from sub-Saharan Africa, we investigated the prevalence and associations of the MetS amongst recent-onset SLE patients.

METHODS: A cross-sectional study of recent onset (<5 years disease duration) patients with SLE meeting the SLICC SLE classification criteria. The MetS was defined by Joint Interim Statement criteria. Clinical and demographic data and a Functional Assessment of Chronic Illness Therapy score and the 36-Item Short-Form Healthy Survey were completed.

RESULTS: Of 75 patients, the mean age was 37.1 (11.7) years, disease duration was 30.8 (23.6) months, 65 (86.7%) were female, 68.0% were of mixed ethnic ancestry and 29.3% were Black Africans. The mean SLEDAI score was 0.9 (1.6). The prevalence of MetS was 40.0%, and age and body mass index were the only significant features associated with MetS ($p = 0.003$ and 0.001 respectively). Increased waist circumference (WC) was the most frequently observed feature, present in 92.9% of MetS patients. Patients with an elevated WC were 32.5 times more likely to have MetS.

CONCLUSION: This study shows a high prevalence of MetS amongst South Africans with recently diagnosed SLE. This calls for aggressive strategies to reduce the prevalence of Mets and atherosclerotic cardiovascular disease. Waist circumference is a useful and cost-effective screening tool to identify SLE patients at risk of MetS.

Keywords: Systemic Lupus Erythematosus; Metabolic Syndrome; Waist Circumference; Africa

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DEDICATION

I dedicate this MMED to all of my family for their support and encouragement through my studies.

LIST OF TABLES

ACRONYMS AND ABREVIATIONS

ALUGEN: African Lupus Genetics Network

ASCV: atherosclerotic cardiovascular events

CHD: coronary heart disease

CVD: cardiovascular disease

EPCs: endothelial progenitor cells

IDF: International Diabetes Federation

HDL-C: high density lipo-protein cholesterol

JIS: Joint interim statement

LDL-C: low density lipo-protein

MetS: metabolic syndrome

NO: nitric oxide

PWV: pulse wave velocity

SLE: systemic lupus erythematosus

SLICC criteria: Systemic Lupus International Collaborating Clinics

SLEDAI: Systemic Lupus Disease Activity Index

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

Systemic lupus erythematosus is a multi-systemic autoimmune disease with numerous clinical manifestations, and a spectrum of severity as well as alternating phases of remission and flares. It commonly affects the skin, joints, kidneys and neurological system.(1) The 5-year survival of patients with SLE has improved from 50% in 1950 to over 95% in 2010.(2). Despite advances in therapies and improved outcomes in the last few decades, mortality and morbidity associated with SLE remains 3 times higher than that of age- and sex-matched healthy persons(3). Several studies have shown that lower socioeconomic status is related to higher morbidity and mortality patients with SLE(4) (5, 6)

As described by Urowits in 1972, mortality amongst SLE patients has a bimodal pattern. Early deaths were caused by active inflammation of major organs, particularly renal and neurological disease, together with infection, and the late deaths in the disease (a mean 8.6 years after symptom onset) were attributable to atherosclerotic cardiovascular (ASCV) events (7). Subsequent studies have confirmed this increased risk of ASCV disease in SLE, particularly amongst young females (8, 9). Manzi et al showed that the incidence of myocardial infarction in women with SLE aged 35-44 years is over 50 times greater than in women of similar age (10).

The explanation for the marked increase in risk for ASCV in SLE is probably multifactorial and may differ for cardiovascular and cerebrovascular events. Immune complex–induced endothelial damage, vasculitis, antiphospholipid antibody–induced thrombosis, Libman-Sacks endocarditis, hypertension from renal involvement or corticosteroid therapy, and corticosteroid-induced central obesity, hyperglyceamia, or hypercholesterolemia are likely to all contribute (11).

The ATP111 Framingham risk score is used to estimate the 10-year risk for ASCV including coronary heart disease, stroke, transient ischemic attack and heart failure (12) and is recommended as a tool to guide the management of dyslipidaemia by the South African (SA) Heart Association and Atherosclerotic Society of SA (13). However, it has become clear that the risk for ASCV in SLE patients cannot be fully explained the traditional Framingham risk factors (14, 15).

Several studies have suggested that impaired endothelial function is the principal driving force behind the accelerated atherosclerosis in SLE (16, 17). Patients with clinically quiescent SLE have also been shown to have reduced small artery elasticity, resulting in impaired endothelial function (14). The most recent literature has focused on endothelial progenitor cells (EPCs). These EPCs play a key role in the repair of vascular damage, and it has been suggested that decreased numbers of this population are associated with an increased risk of ASCV Disease, and even with preclinical atherosclerosis (18). The numbers and function of peripheral blood EPCs amongst SLE patients are significantly reduced suggesting that this cell population could potentially be involved in the development of premature atherosclerosis in this disease.

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities associated with central adiposity and insulin resistance that increase the risk of ASCV.The key components of MetS are abdominal obesity, atherogenic dyslipidaemia, raised blood pressure and insulin resistance with glucose intolerance (19). There are various criteria used to define the MetS (Table 1). The recommendations set by the Joint Interim Statement (JIS) are the most preferred as they have been broadened to include cut-off values for both Europeans and non-Europeans as a consensus definition which can be adapted for the African population (20).

Mok et al reported an increased risk of premature ASCVD after adjustment for age and other vascular risk factors not included in the MetS (21).

At first glance, ASCV is a disease of affluence, and was once uncommon in sub-Saharan Africa. Over the last three decades, economic and lifestyle transformation including urbanisation and adoption of "western lifestyle" have taken place in sub-Saharan Africa. Thus, despite widespread poverty, the prevalence of the MetS is increasing and ASCV is emerging as a major cause of mortality (22) .

A high prevalence of MetS has been documented in an urban mixed ethnic ancestry population in the Western Cape. According to the JIS definition, 62% of adults over 31 years had MetS, with females particularly affected (23). Elsewhere, then Mets has been shown to have an inverse relationship with low socio-economic status (24). One factor contributing to this may be the dietary choices of low income households such as energy-dense, highly palatable foods that provides maximum calories per volume at the least cost. Interestingly, low house hold income may increase the risk of MetS in gender specific manner, with women more affected than men(25),(26).

Several studies have reported a higher prevalence of MetS amongst SLE patients compared to the general population (Table 2). Studies from first world European countries have report a prevalence of MetS ranging between 16% and 22%, whereas developing countries have a much higher prevalence of 38.2% Puerto Rico and as high as 45.2% in Brazil(26) (27, 28).

Systemic Lupus Erythematosus is a state of chronic inflammation due to over-production of pro-inflammatory factors including interleukin-6(IL-6), C-reactive protein(CRP), leptin, plasminogen activator inhibitor -1 (PAI-1), erythrocyte sedimentation rate (ESR) and tumour necrosis factor alpha (TNF -a) .

There are various mechanisms implicated in the pathogenesis of endothelial dysfunction in MetS. Recent attention has focused on the imbalance of arterial vasoactive substances. Decreased nitric oxide (NO) availability appears to play a major role and may result from reduced NO production and/or increased inactivation by reactive oxygen species(29, 30) In addition, reduced availability of other vasodilating agents (such as prostacyclin and endothelium-derived hyperpolarizing factors) and/or increased production or activity of vasoconstrictive substances (including endothelin-1 and angiotensin II) are also implicated. All the components of MetS can individually impair endothelial function(29, 31). Some studies have reported higher levels of these inflammatory markers such as homocysteine and CRP in patients with SLE with MetS (21, 32).

Impaired peripheral blood EPC function is associated with the MetS together with significantly elevated serum uric acid and inflammatory biomarkers, including homo-cysteine, IL-8, sICAM-1 or complement molecules, in SLE patients with MetS (18). A positive association between increased arterial stiffness and MetS has been reported. One recent study demonstrated that SLE patients with and without MetS differed significantly regarding arterial stiffness, with the average aortic pulse wave velocity (PWV) significantly higher in the MetS group compared to the non-MetS group (33). There is a close link between the presence of MetS and increased arterial stiffness, even when PWV determination was adjusted for age and BP.(9) . SLE patient with MetS have higher levels apolipoprotein-B(Apo-B) which has been shown to be an independent predictor of arterial stiffness.(34). MetS and its components may influence levels of adipokines such leptin(35) . Amongst SLE patients with Mets, increased leptin levels have close correlation with subclinical atherosclerosis as measured by carotid intima media thickness (8).

Current treatment recommendations for the management of MetS are targeted at the general population and focus on two key therapeutic goals. These include weight management and increasing physical activity together with optimal medical management of cardiovascular risk factors if they persist despite lifestyle modification (36, 37). The risk of development of type 2 diabetes and the levels of risk factors for ASCV can be substantially reduced by lifestyle modification. In a study conducted by The Diabetes Prevention Program, both intensive lifestyle intervention and the addition of metformin therapy were effective for prevention of MetS in patients who did not have the syndrome at baseline(38). Metformin may also reduce the incidence of diabetes- related endpoints such as fatal myocardial infarction or sudden death, fatal stroke, or death from peripheral vascular disease, renal disease and hyper/hypoglycaemia.(39) Although not strictly addressing the MetS, the 4S trial of lipid lowering with simvastatin showed that amongst patients with elevated serum LDL cholesterol and established coronary disease, those with MetS had both the highest risk of major coronary events and greatest benefit (48% risk reduction) from statin therapy (40, 41).

There is some debate regarding the use of low dose aspirin in patients with SLE and MetS as primary prophylaxis. It has been suggested that patients with SLE should receive low-dose aspirin prophylaxis only if they have certain risk factors such as risk factors for ASCVD or previous history of ASVD or positive anti-phospholipid antibodies(42). Reinforcing this, a recent Italian study showed that low-dose aspirin is a safe treatment and may be beneficial in the primary prophylaxis of ASCV events in SLE patients.)(43).

More research is needed to evaluate the role of lifestyle modification and pharmaco-prevention for diabetes in SLE patients with or without Mets, and interventions focusing specifically on managing the MetS and reducing ASCVD in patients with SLE. To date, there are no published studies on MetS in sub-Saharan Africans with SLE. This study aims to determine the prevalence and associations of MetS in adults with recent onset SLE in the Western Cape, South Africa.

Table 1: Comparison of the diagnostic criteria for the Metabolic Syndrome

Components	NCEP-ATP III(44)	AHA/N(36)	IDF(45)	JIS(20)
Number of	≥3	≥3	Central obesity	≥3
Fasting plasma	≥6.1 mmol/L	≥5.6 mmol/L	≥5.6 mmol/L	≥5.6 mmol/L
Waist	≥102 cm (men)	≥102 cm (men)	≥94 cm (men)	≥94 cm (men)
	≥88 cm (women)	≥88cm (women)	≥80 cm (women)	≥80 cm (women)
Blood pressure	≥130/85 mm Hg	≥130/85 mm Hg or receiving treatment	≥130/85 mm Hg or receiving treatment	≥130/85 mm Hg or receiving treatment
Triglycerides	≥1.7 mmol/L	≥1.7 mmol/L or	≥1.7 mmol/L or	≥1.7 mmol/L or
High-density lipoprotein cholesterol	<1.0 mmol/L (men) <1.3 mmol/L (women)	<1.0 mmol/L (men) <1.3 mmol/L (women) or receiving treatment	<1.0 mmol/L (men) <1.3 mmol/L (women) or receiving treatment	<1.0 mmol/L (men) <1.3 mmol/L (women) or receiving treatment

MetS: Metabolic syndrome; IDF: International Diabetes Federation; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; JIS: Joint Interim Statement on MetS ; AHA/NHLB: American Heart Association /National Heart, Lung ,and Blood Institute

Table 2: Global prevalence of MetS in patients with SLE

Country, year of publication	MetS criteria	Age (SD) (yrs)	Disease duration - mean (yrs)	Prevalence MetS n, (%)
Iran,2018(46)	NCEP/ATPIII IDF	41.0 (12.2)	6.5	33/73 (45.2) 34/73 (46.6)
Italy,2017(47)	IDF	47.5 (14.1)	9.9	34/100 (34.0)
(48)	Metanalysis	NA	NA	26 (CI 0.25-0.27)
Brazil,(49)	NCEP/ATPII	41.7(2.5)	11.9	66/146(45.2)
Turkey,(50)	NCEP/ATPIII	40.2(13.5)	4.6	58/311(19.0)
Multinational,2015 (51)	JIS	34.9 (13.6)	0.5	439/1150 (38.2)
(52)	WHO 1999 definition Consensus definition for Asian Indian Adults	28.7(6.8) 28.7(6.8)	2.0 2.0	15/82(18.2) 24/82(29.2)
(53)	JIS	31.0(5.5)	10.6	23/103(22.3)
Egypt, 2015 (54)	(NCEP/ ATP III)	32.9 (8.5)	3.4	12/30 (40.0)
Peru,2014 (55)	JIS	44.6 (12.9)	7.6	42/117 (44.4)
China,2013 (56)	JIS	34.1 (11.1)	2.9-	40/116 (34.2)
Egypt, 2013 (57)	(ATP III)	30.2 (8.3)	5.8	34/92 (36.9)
UK,2011(58)	JIS	48.0 (42-58)	8.5	60/200 (30.0)
Italy,(28)	IDF	38.8(11.2)	8.5	52/162(32.1)
Spain (26)	AHA/NHLB	43.6(13)	8.7	87/204(38.2)
Nederlands,2008 (59)	AHA/NHLB	39.0 (12)	6.6	22/14 (16.0)

Abbreviations: MetS: Metabolic syndrome ; IDF: International Diabetes Federation ; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; WHO: World Health Organisation; JIS: Joint Interim Statement on MetS ; AHA/NHLB: American Heart Association /National Heart, Lung ,and Blood Institute

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

High Prevalence of Metabolic Syndrome in South African Systemic Lupus Erythematosus patients

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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ABSTRACT

INTRODUCTION: Patients with systemic lupus erythematosus (SLE) are at increased risk of the metabolic syndrome (MetS) and its complications. In the absence of published studies from sub-Saharan Africa, we investigated the prevalence and associations of the MetS amongst recent-onset SLE patients.

METHODS: A cross-sectional study of recent onset (<5 years disease duration) patients with SLE meeting the SLICC SLE classification criteria. The MetS was defined by Joint Interim Statement criteria. Clinical and demographic data and a Functional Assessment of Chronic Illness Therapy score and the 36-Item Short-Form Healthy Survey were completed.

RESULTS: Of 75 patients, the mean age was 37.1 (11.7) years, disease duration was 30.8 (23.6) months, 65 (86.7%) were female, 68.0% were of mixed ethnic ancestry and 29.3% were Black Africans. The mean SLEDAI score was 0.9 (1.6). The prevalence of MetS was 40.0%, and age and body mass index were the only significant features associated with MetS (p = 0.003 and 0.001 respectively). Increased waist circumference (WC) was the most frequently observed feature, present in 92.9% of MetS patients. Patients with an elevated WC were 32.5 times more likely to have MetS.

CONCLUSION: This study shows a high prevalence of MetS amongst South Africans from the Western Cape who were mostly of mixed ancestry, with recently diagnosed SLE which was uncomplicated and had low disease activity . This calls for aggressive strategies to reduce the prevalence of Mets and atherosclerotic cardiovascular disease. Waist circumference is a useful and cost-effective screening tool to identify SLE patients at risk of MetS.

Keywords: Systemic Lupus Erythematosus; Metabolic Syndrome; Waist Circumference; Africa

BACKGROUND

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease, associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), with an incidence of myocardial infarction in affected women aged 35-44 years over 50 times greater than in healthy women of the same age (10). Recent studies have reported an increased risk of premature cardiovascular disease after adjustment for age and traditional vascular risk factors (8, 9, 21, 60).

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities associated with central adiposity and insulin resistance (45). This syndrome leads to endothelial dysfunction, arterial stiffness and accelerated ASCVD (18, 33, 61). Patients with systemic lupus erythematosus (SLE) have been shown to have a higher burden of the MetS than healthy controls.(53, 58, 62, 63)

At first glance, MetS was perceived as a disease of affluence, and was once uncommon in sub-Saharan Africa(64). Over the last three decades, lifestyle changes associated with urbanisation have taken place and, despite widespread poverty, the prevalence of the MetS is increasing and ASCV is emerging as a major cause of mortality (22). Recently, a high prevalence of MetS was documented in an urban population of mixed ethnic ancestry in the Western Cape where 62.0% of adults over 31 years had MetS, with females particularly affected (23).

To date, there are no published studies on MetS in sub-Saharan Africans with SLE. This study was undertaken to determine the prevalence and associations of MetS in adults with recent onset SLE in the Western Cape, South Africa.

Patients and Methods

This cross-sectional study recruited patients from the rheumatology clinic in a state-sector academic hospital as part of the African Lupus Genetics Network, a prospective database of SLE patients (65). All patients met the following inclusion criteria: adults (≥18 years); symptom onset within the last 5 years; and fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) SLE criteria (66). The exclusion criteria were: pregnancy or lactating .

Approval for the study was obtained from the University of Cape Town Human Research Ethics Committee, and all patients signed informed consent before participating in the study.

Demographic data, clinical details including comorbidities, therapy and bio-morphometric details were collected. Serum lipid lipogram results including total cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were documented. In addition, patients completed a Functional Assessment of Chronic Illness Therapy (FACIT) score measuring fatigue and the 36-Item Short-Form Health Survey (SF-36)as a general measure of health-related quality of life (HRQoL)(67). The MetS was defined according to the JIS criteria, using WC cut-offs of male >94 cm, female> 80 cm (20).

Statistical methods

The Students *t*-test was applied to compare continuous variables between groups, except where the data showed a non-normal distribution, in which case the Wilcoxon rank sum test was used. The Chi-square test, or where indicated, the 2-tailed Fishers' exact test was used in the case of categorical variables. A bivariate logistic regression model was constructed to assess the association between specific variables (socio-demographic, clinical and treatment) and MetS. Significant variables found in the univariate analyses and chi-square contingency tests were entered the logistic regressions. A p-value of 0.05 was considered significant. Statistical analyses were done using SPSS version 24.

Results

Of 75 patients, 86.7% were female, and of these 58.5% were premenopausal, the mean (SD) age was 37.1 (11.7) years and disease duration was 30.8 (23.6) months (Table 1). In terms of ethnicity, 68.0% were of mixed ethnic ancestry and 29.3% were black Africans and 2.7% were Caucasian. Patients were of poor socio-economic background: the mean (SD) highest level of schooling was 10.0 (2.6) years, and 30.7% were unemployed.

The SLE disease activity index (SLEDAI) and Systemic Lupus International Collaborating Clinics damage index were low (0.9 (1.6) and 0.3 (0.7) respectively). The SF-36 scores showed poor physical and mental health, with low FACIT scores suggesting a high burden of

fatigue,a sedentary lifestyle may have contributed to the background prevalence of metabolic syndrome . The mean (SD) body mass index (BMI) was 30.3 (23.6) kg/m^2, over a third of patients were smokers. Two thirds had been exposed to corticosteroids.

The prevalence of MetS in this cohort was 40.0%, and patients with MetS were significantly older than patients without MetS (mean age 41.9 vs 33.8 years, p =0.003), and had a higher BMI (mean BMI 30.3 vs 25.7 kg/cm^2, p =0,001) (Table 1). More patients in the MetS group were unemployed (47.8% vs 26.7%), although this did not reach statistical significance.

The feature of the MetS most commonly encountered was an elevated WC, present in 92.9% of those with MetS (Table 2). Elevated TG and low HDL-C were also significantly associated with the MetS (p <0.001 and 0.008 respectively). Multivariate analysis showed that only elevated waist circumference, elevated blood pressure, and low HDLC were independently associated with the MetS, encountered in 74.1% of MetS patients (p < 0.001, Nagelkerke R^2 =0.74).

Discussion

This study,is the first study to our knowledge assessing a cohort of SLE patients with MetS in sub-Saharan African, shows that 40.0% of South African patients in the Western Cape with recent-onset SLE fulfilled criteria for the MetS. This high prevalence of the MetS is similar to that reported in low and middle-income countries (LMIC) of patients with SLE with disease duration less than 10 years (Table 3). A lower prevalence of MetS has been reported in higher income European countries. While these differences may reflect variations in the diagnostic criteria, other explanations might include genetic susceptibility or environmental factors,sedentary lifestyle and a high calorie diet (48, 58).

Most of the patients in our study were young women of poor socioeconomic status, with over a third of patients unemployed, and dependant on a state disability grant. Several other studies have shown that a lower socioeconomic level is associated with MetS (27, 68). The high prevalence of smoking (36%) is a concern. A South African study demonstrated a high smoking prevalence and a 50% higher overall smoking-related mortality in patients of

mixed ethnic ancestry compared to other race groups, with ASCVD a major cause of death (69).

Many studies have looked at the factors that predispose SLE patients to developing MetS. The present study found only age and BMI to be significant, with no association with disease activity, damage scores or therapy. A recent study in South India, no association was found between the MetS, SLE disease activity or damage scores (52). Several studies have shown no association with steroid use (28, 62, 63). In contrast, a Brazilian study of premenopausal SLE women showed that MetS was associated with a higher cumulative dose of steroids (53). In addition, we demonstrated no association between MetS and HRQoL or fatigue. A recent Italian study demonstrated that SLE patients with MetS report low mood and physical inactivity, and have a poor HRQoL in both mental and physical components (47).

Elevated WC was the most common component of the MetS. In our study 57.3 % of the total number of patients with elevated WC had MetS, and patients with an elevated WC were 32.5 times more likely to have MetS than those with a normal WC. Elsewhere, studies of SLE patients have shown WC to be an important feature of the MetS (62, 63, 70). Similarly, in the general population of the Western Cape, elevated WC was the most commonest feature of the MetS, and was shown to be a better predictor than BMI of ASCVD risk in the general population in a US cohort of patients (23, 71). Hence, WC could be a useful and cost-effective screening tool to identify those at risk of MetS.

Dyslipidaemia, specifically a reduced HDL-C, was the second most common occurring feature in our study, again similar to the findings of other studies. Of concern, HDL can lose its anti-inflammatory properties in states of chronic inflammation, and instead become pro-inflammatory (piHDL). In a study in California, 45.0% of women with SLE were found to have the dysfunctional piHDL, increasing the risk of subclinical atherosclerosis (72).

Limitations of our study include the cross-sectional design, the small number of patients included, and the lack of a healthy control group. In addition, we were unable calculate patients' cumulative prednisone dose. We plan to expand and follow this cohort for the development of ASCVD.

In conclusion, we have shown a high prevalence of MetS amongst South Africans in the Western Cape with recently diagnosed SLE. This, together with the high prevalence of cigarette smoking, and SLE disease itself, infers a particularly significant risk of ASCVD. Future interventional studies addressing modifiable risk factors such as weight loss, smoking cessation and physical activity in this population are planned. Waist circumference is a useful screening tool for identifying those at risk of MetS and should be incorporated into the routine assessment of SLE patients.

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Table 1 Demographic and clinical characteristics of patients with SLE according to the presence or absence of metabolic syndrome

Features	Overall cohort (n=75)	MetS (n= 30)	No MetS (n= 45)	*p-value**	OR (95% CI)**
Age (years)(mean, SD)	37.1 (11.7)	41.9 (10.1)	33.8 (11.6)	0.003	
Female n (%)	65 (86.7)	28 (93.3)	37 (56.9)	ns	3.0 (0.6 – 15.3)
Postmenopausal n (%)	5 (7.7)	4 (16.0)	1 (2.5)	ns	
Ethnicity (self-reported)- n (%)					
Black African	22 (29.3)	7 (23.3)	15 (33.3)	ns	
Mixed ancestry	51 (68.0)	22 (73.3)	29 (64.4)	ns	
White	2 (2.7)	1 (3.3)	1 (2.2)	ns	
Disease duration (months)(mean, SD)	30.8 (23.6)	29.9 (18.8)	31.5 (27.0)	ns	
Highest level schooling (years) (SD)	10.0 (2.6)	9.9 (2.7)	10.1 (2.6)	ns	
Unemployed n (%)	23 (30.7)	11 (47.8)	12 (26.7)	0.10	1.6 (0.6 – 4.3)
Body Mass Index (kg/cm^2) (mean, SD)	27.6 (5.9)	30.3 (4.7)	25.7 (6.1)	0.001	
Cigarette smoking (current) n (%)	27 (36.0)	12 (40.0)	15 (34.1)	ns	1.3 (0.5 – 3.4)
SLEDAI score (mean, SD)	0.9 (1.6)	0.7 (1.1)	1 (1.8)	ns	
SLICC damage index (mean, SD)	0.3 (0.7)	0.3 (0.5)	0.3 (0.8)	ns	
Corticosteroids ever prescribed n (%)	50 (66.6)	20 (66.6)	30 (66.6)	ns	0.9 (0.3 – 2.4)
Corticosteroid dose n (%)				ns	0.7 (0.2 – 2.7)
Low (≤ 10 mg)	37/48 (77.1)	17/20 (85.0)	20/28 (71.4)	ns	
High (>10 mg)	11/48 (22.9)	4/20 (20.0)	7/28 (25.0)	ns	
SF-36 PCS (mean score) (mean, SD)	39.1 (19.8)	39 (20.1)	39.2 (19.9)	ns	
SF-36 MCS (mean score) (mean, SD)	43.1 (24.7)	41.1 (26.9)	44.5 (23.3)	ns	
FACIT score (mean, SD)	28.1 (12.4)	26.5 (12.8)	29.2 (12.2)	ns	

*Comparing patients with MetS to those without MetS

** Odds Ratio only reported for categorical variables

ns: not significant; MetS: Metabolic syndrome; SLEDAI: SLE disease activity index; SLICC: Systemic Lupus International Collaborating Clinics; MCS Mental Composite Score; PCS: Physical Composite Score FACIT: Functional Assessment of Chronic Illness Therapy;

Table 2: **Frequency of the different components of metabolic syndrome in SLE patients**

Features	**Overall cohort n=75**	**MetS patients n=30**	**Non MetS patients n =45**	***Univariate analysis****		***Multivariate analysis****	
				OR (95% CI)	**p-value**	***OR (95% CI)***	**p-value**
Elevated waist circumference n (%)	43 (57.3)	26 /28 (92.9)	10/35 (28.6)	32.5 (6.5-163.3)	<0.001	0.01 (0.01-0.61)	0.03
Elevated triglycerides or on drug therapy n (%)	18/74 (24.3)	15/29 (51.7)	5/39 (12.8)	7. 3 (2.2-23.9)	<0.001	0.07 (0.01 – 1.36)	0.08
Reduced HDL-C or on drug therapy n (%)	35 (46.5)	18/26 (69.2)	14/39 (35.9)	4.0 (1.4-11.6)	0.008	0.04 (0.0.1 – 0.85)	0.04
Elevated blood pressure or on drug therapy n (%)	20 (26.9)	15 (50.0)	9/44 (20.5)	3.9 (1.4-10.8)	0.008	0.04 (0.01 – 1.03)	0.05
Elevated fasting glucose or drug therapy n (%)	3 (4.3)	3 (10.0)	1/44 (2.3)	4.8 (0.5-48.3)	ns		

*Comparing patients with MetS to those without

MetS: Metabolic syndrome; HDL-C: High Density Lipoprotein Cholesterol; SLE: Systemic Lupus Erythematosus

Table 3: Global prevalence of MetS in patients with SLE with recent-onset SLE (disease duration less than 10 years)

Country, year of publication	MetS criteria	Age (SD) (yrs)	Disease duration- mean (yrs)	Prevalence MetS n, (%)
Iran,2018(46)	NCEP/ATPIII IDF	41.0 (12.2)	6.5	33/73 (45.2) 34/73 (46.6)
Italy,2017(47)	IDF	47.5 (14.1)	9.9	34/100 (34.0)
Multinational,2015 (51)	JIS	34.9 (13.6)	0.5	439/1150 (38.2)
Egypt, 2015 (54)	(NCEP/ ATP III)	32.9 (8.5)	3.4	12/30 (40.0)
Peru,2014 (55)	JIS	44.6 (12.9)	7.6	42/117 (44.4)
China,2013 (56)	JIS	34.1 (11.1)	2.9	40/116 (34.2)
Egypt, 2013 (57)	(ATP III)	30.2 (8.3)	5.8	34/92 (36.9)
UK,2011(58)	JIS	48.0 (42-58)	8.5	60/200 (30.0)
Nederlands,2008 (59)	AHA/NHLB	39.0 (12)	6.6	22/14 (16.0)

MetS: Metabolic syndrome ; IDF: International Diabetes Federation ; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; JIS: Joint Interim Statement on MetS ; AHA/NHLB: American Heart Association /National Heart, Lung ,and Blood Institute

CHAPTER 3 APPENDICES

Questionnaire/data capture instrument

Folder number:

Name and surname

Contact details:

Demographics

- SEX:
- DOB :
- AGE:
- ETHNIC GROUP:
- HIGHEST LEVEL OF EDUCATION
- EMPLOYEMENT

Clinical background

DATE OF SYMPTOM ONSET

DATE OF DIAGNOSIS

MENOPAUSAL STATUS

SMOKER HISTORY

HYPERTENSION :

Clinical assessment

HIEGHT: WEIGHT: kg BMI kg/m^2

WAIST CIRCUMFERENCE: cm

HIP CIRCUMFERENCE: cm

HIP –WAIST CIRC :

BLOOD PRESSURE SYSTOLIC/ DYSTOLIC _____mmHg

TOTAL CHOLESTEROL mg/dl TRIGLYCERIDES _____mmHg

HDL- CHOLESTEROL _____mmHg HbA1c _____mmol/l

Treatment /medication

- CHLOROQUINE
- STATIN USE
- PREDNISONE USE
- LOW DOSE ASPIRIN USE

Consent form

Study Title: Metabolic Syndrome in patients with systemic lupus erythematosus attending Groote Schuur Hospital?

I, _____ , agree to participate in this study that will examine details of my medical history(especially sugar diabetes and high blood pressure , together with my weight, waist and hip measurements , height and body mass index , calculated as weight in kilograms (kg) and divided by the square height in metres - kg/m^2)

I understand that this study will also look at the results of blood samples taken to measure total cholesterol, high density lipo-protein cholesterol (HDL), low density lipo-protein(LDL) and triglycerides .

I understand that this test is required as part of my routine visits to the clinic, and is not performed only for this study.

The results of this study will be made known to me, via my doctor, in accordance with the relevant protocol, if and when available.

In addition, I authorise that they may be made known to other doctors involved in my care.

I have been informed that:

- There are risks and benefits associated with analysis and these have been explained to me.
- Even under the best conditions, current technology of this type is not perfect and could lead to incorrect results.
- Where biological material is used for research purposes, there may be no direct benefit to me.

I understand that I may withdraw my consent for any aspect of the above at any time without this affecting my future medical care.

ALL OF THE ABOVE HAS BEEN EXPLAINED TO ME IN A LANGUAGE THAT I UNDERSTAND AND MY QUESTIONS ANSWERED BY:

Ethics approval letter from the Faculty Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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27 July 2015

HREC REF: 398/2015

Dr B Hodkinson
Department of Rheumatology
J-Floor
OMB

Dear Dr Hodkinson

PROJECT TITLE: METABOLIC SYNDROME IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ATTENDING GROOTE SCHUUR HOSPITAL (MMed-candidate-Dr A Nkabane)

Thank you for your letter dated 20 July 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th July 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Dr Avela Nkabane will be involved in this project.

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:398/2015

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v. In keeping with the latest guidelines of the International Committee of Medical Journal Editors, each author's contribution to the paper is to be quantified;
vi. Acknowledgements;
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x. Tables (each table complete with title and footnotes);

xi. Figure legends;
xii. Appendices (if relevant).

Figures and Supporting Information should be supplied as separate files.

Authorship

Please refer to the journal's Authorship policy in the Editorial Policies and Ethical Considerations section for details on author listing eligibility.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the 'Conflict of Interest' section in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Abstract

Please refer to the section on Manuscript Categories and Requirements above for information regarding which article types require abstracts.

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Please provide 5-7 keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at www.nlm.nih.gov/mesh.

Main text

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References

All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should be superscript numbers.

Submissions are not required to reflect the precise reference formatting of the journal (use of italics, bold etc.), however it is important that all key elements of each reference are included. Please see below for examples of reference content requirements.

Sample references follow:

Journal article

1. Needleman P, Isakson PC (1997) The discovery and function of COX-2. J Rheumatol 24,6–7.

Book

2. Munthe E (ed.) The Care of Rheumatic Children. European League Against Rheumatism, Basel, Switzerland.

Chapter in a book

3. Croft P (1993) Soft tissue rheumatism. In: AJ Silman, MC Hochberg (eds) Epidemiology of the Rheumatic Diseases, pp. 375–421. Oxford University Press, Oxford.

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

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Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted.

Supporting Information

Supporting information is information that is not essential to the article but that provides greater depth and background. It is hosted online, and appears without editing or typesetting. It may include tables, figures, videos and datasets

Note, if data, scripts or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

PROTOCOL

PREVALENCE OF METABOLIC SYNDROME IN PATIENT WITH SLE IN THE WESTERN CAP

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BACKGROUND

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities associated with central adiposity and insulin resistance that increase the risk of atherosclerotic cardiovascular events (ASCV).The key components of MetS are abdominal obesity, atherogenic dyslipideamia, raised blood pressure and insulin resistance with glucose intolerance.(45) In the developed world, patients with Systemic lupus erythematosus (SLE) have been shown to have a higher burden of the metabolic syndrome (MetS) than healthy controls.

A bimodal pattern of mortality in SLE was described by Urowits in 1972, based on his observations of a Canadian cohort of SLE patients followed over 10 years(7).Active inflammation of major organs, particularly renal and neurological disease, together with infection, caused death early in the disease. Late deaths (a mean 8.6 years after symptom onset) were attributable to atherosclerotic cardiovascular (ASCV) events**.** Subsequent studies have confirmed this increased risk of ASCV disease in SLE, particularly amongst young females. Manzi et al (10)showed that the incidence of myocardial infarction in women with SLE aged 35-44 years is over 50 times greater than in women of similar age.

Metabolic syndrome may lead to endothelial dysfunction and accelerated ASCVD in SLE patients. Recently, MetS-associated impaired peripheral blood endothelial progenitor cell function is described(18) together with significantly elevated serum uric acid and inflammatory biomarkers, including homo-cysteine, IL-8, sICAM-1 or complement SLE patients with MetS. Not surprisingly, SLE patients with MetS have been shown to have arterial stiffness(18, 33, 61).Of major concern, SLE is associated with an increased risk of premature cardiovascular disease due to accelerated atherosclerosis over and above traditional risk factors included in the MetS.Mok and colleagues reported an increased risk of premature cardiovascular disease after adjustment for age and other vascular risk factor not included in the syndrome(21)

At first glance, MetS is a disease of affluence, and was once uncommon in sub-Saharan Africa. Over the last three decades, economic and lifestyle transformation including urbanisation and adoption of “western lifestyle” have taken place in sub-Saharan Africa. Thus, despite widespread poverty, the prevalence of the MetS is increasing and ASCV is emerging as a major cause of mortality(22). A high prevalence of MetS has been documented in an urban population of mixed ancestry in the Western Cape(23) according to the Joint Interim Statement (JIS) of the IDF/NHLBI/AHA/WHF/IAS/IASO definition (73), 62% of adults over 31 years had MetS, with females particularly affected.(74)

To date, there are no published studies of the prevalence or associations of the MetS in sub-Saharan Africans with SLE. This study will be undertaken to determine the prevalence of MetS in adults with SLE with recent onset (<5years d duration).

OBJECTIVES:

Primary Objective

1. To measure the prevalence and associations of the MetS a defined by Joint Interim Statement (JIS) in SLE patients with recent onset SLE (<5 years disease duration).

The secondary objectives are:

2. To document the treatment practices of patients with SLE, use of low dose aspirin and the use chloroquine.

PATIENTS AND METHODS

This cross-sectional study will enrol 105 patients onto a prospective SLE database, ALUGEN (African Lupus Genetics Network). Patients will be enrolled from Groote Schuur Hospital (GSH) rheumatology outpatient department, and will meet the following inclusion criteria: SLE according to SLICC 2012 criteria(66),age greater than 18 years old, SLE diagnosis less than or equal to 5 years ago and signed informed consent to participate in the study.

Demographic data, clinical details of organ-specific involvement, comorbidities, therapy and bio-morphometric details will be collected with a special focus on the following factors:

1. Participants details and contact details (name, surname date of birth, gender and ethnic background (self-reported)
2. Disease history including past or present history of smoking, family history of premature coronary heart disease
3. Clinical features of organ involvement (constitutional, skin, musculoskeletal, cardiovascular, neuropsychiatric, renal, ocular, haematological, immunological, and gastrointestinal system.
4. Obstetric history and menopausal status (females only)
5. Medication details including the current use and doses of corticosteroids (prednisone), chloroquine, statin and low dose aspirin.

MetS will be defined according to the JIS criteria(20)

STATISTICAL METHODS

The Students t test will be applied to compare continuous variables between groups, except where the data shows a non-normal distribution, in which case the Wilcoxon rank sum test will be used. The Chi-square test, or where indicated, the 2-tailed Fishers' exact test will be used in the case of categorical variables. Spearman correlation coefficients will be applied to assess correlations between continuous variables. We will perform Multivariate analysis using stepwise backward logistic regression, and demographic and baseline variables with a p-value ≤ 0.15 in the univariate analysis will be included in the model. A p-value of 0.05 will

be considered significant. All statistical analyses will done using Stata 10 software (StataCorp, USA).

ETHICAL CONSIDERATIONS

Ethical approval for the ALUGEN database has already been obtained from the joint Groote Schuur Hospital and University of Cape Town Research Ethics Committee (REC) (535/2010). An amendment has been be submitted for this sub-study.

Consent to enter the study will be sought from each participant only after a full explanation has been given, and time allowed for consideration (Appendix A). Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected.

The Principal investigator and all investigators on the study will preserve the confidentiality of participants taking part in the study in compliance with data protection legislation. Anonymity will be ensured with the use of a master code which will be kept in a separate secure filing cabinet. All computers will be password protected.

TIMING:

The study will run retrospectively from September of 2015.

- Protocol will be submitted to the Postgraduate Committee in April 2016.
- Ethics submission will be in May 2016.
- Data analysis will be completed in January 2018.
- Manuscript preparation and completion will be accomplished by 30th of

July 2018 for submission for publication.

The study will be carried out according to the following Gantz chart:

2015- 2017	April	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol assessment									
Data Collection									
Data analysis and write up									

FUNDING:

There are no anticipated costs to the hospital or participating patients arising from this study. Blood investigations and physical assessments performed at the SLE clinics on all patients as part of routine clinical care. Statistical analysis and any administrative costs (printing, photocopies and telephone calls) will be covered by an NRF Thuthuka grant held by Prof B Hodkinson for the ALUGEN project.

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