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PAPER

An analysis of the metabolic syndrome phenotype in systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is associated with an increased risk of coronary heart disease (CHD) not fully explained by classic risk factors. Metabolic syndrome (MetS) is associated with an increased risk of CHD in the general population and whilst its prevalence is increased in SLE, its phenotypic expression may differ. We studied 200 women with SLE and 100 controls and compared the prevalence of MetS and its individual components. We examined whether any SLE features were associated with MetS and whether MetS in SLE patients was associated with carotid plaque. Patients with SLE were more likely to meet the MetS criteria (age-adjusted OR 2.1 (1.1–3.8)). However, this was not due to increased central obesity (median waist circumference 84 cm vs. 82 cm, $p = 0.65$) but rather increased prevalence of hypertension ($p < 0.01$) and low HDL-cholesterol ($p = 0.01$). In a multivariable analysis, age, disease duration, low complement C3 and corticosteroid use ever, were associated with the presence of MetS in SLE. Overall MetS was not associated with the presence of carotid plaque in either SLE or controls. We have shown that MetS is more prevalent in SLE, but the lupus-MetS phenotype reflects risk factor changes driven by disease activity and steroid exposure, rather than obesity. Reliance on clinical measures of central obesity to consider MetS in SLE is not reliable and continued attention to individual CHD risk factors is recommended. *Lupus* (2011) 0, 1–7.

Key words: atherosclerosis; metabolic syndrome; systemic lupus erythematosus

Introduction

Premature CHD is a significant cause of morbidity and mortality in patients with established SLE.^{1,2} Overall, women with SLE have a five-fold increased risk of CHD events compared with the non-lupus population, rising to a 50-fold increase in younger patients³ and patients with SLE have an increased burden of subclinical atherosclerosis.^{4,5} Classic Framingham risk factors for CHD, although more prevalent in SLE,⁶ do not fully explain this disparity in CHD risk.⁷ SLE should therefore be considered an independent risk factor for CHD.

The increased cardiovascular risk is likely to be multifactorial, and insulin resistance has been implicated.⁸ The recently defined metabolic syndrome (MetS) refers to a clustering of metabolic abnormalities and CHD risk factors in an individual thought to reflect increased adiposity and which acts through insulin resistance to increase the risk of developing both CHD and type 2 diabetes mellitus. The MetS has several current definitions⁹ and a recent criteria set was agreed in an effort to further harmonize the definition.¹⁰ Unlike other definitions this harmonized MetS definition allows the MetS to be defined without central obesity markers being a *sine qua non*.

The presence of MetS is associated with an increased risk of cardiovascular events in the general population,¹¹ although its superiority to existing CHD risk stratification scores is not universally acknowledged.^{12–14} In the context of SLE, little is known about the relative contribution of individual criteria to the overall prevalence of MetS and how this compares with the general population.¹⁵ MetS

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in SLE, a chronic inflammatory disease, may therefore have a different genesis compared with the non-lupus population which will have implications for its management and also our understanding of CHD risk in SLE.

The aim of this study was to compare the prevalence and phenotypic features of MetS in women with SLE and healthy controls. We also aimed to investigate whether inflammatory disease activity and/or therapies for SLE are associated with the presence of the syndrome, and to determine whether MetS is associated with carotid plaque beyond any association with its component features.

Methods

Participant recruitment

White British female subjects with SLE from out-patient clinics across Greater Manchester (Manchester Royal Infirmary, North Manchester General Hospital, Blackburn Royal Infirmary, South Manchester University Hospital and Stepping Hill Hospital, Stockport) were invited to participate in this cross-sectional study, according to a previously described methodology.⁴ Briefly, patients with SLE were included if they were aged >18 years and had been on stable therapy for at least 2 months; pregnant or lactating women were excluded. Patients met ≥ 4 of the 1997 updated ACR criteria for SLE¹⁶ or 3 criteria in the absence of an alternative diagnosis.⁴ Data concerning demographics, lifestyle factors, traditional CHD risk factors, medical history and lupus history were collected using a standard protocol. SLE disease activity and damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K)¹⁷ and the Systemic Lupus International Collaborating Clinics/ACR damage index (SLICC-DI)¹⁸ respectively. Healthy female controls free from any chronic inflammatory disease, of the same ethnicity, and from the same geographical area were recruited using a 'best-friend' system. An older control population was deliberately targeted to allow modelling of factors influencing carotid plaque. The study was approved by the North West Multi-Centre Research Ethics Committee and written informed consent was obtained from each participant.

Definition of MetS

Patients were defined as having MetS according to the 2009 definition quoted in the Joint Interim Statement from the International Diabetes

Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.¹⁰ This harmonizing statement defines MetS as being present if three or more of the following five criteria are present: (1) elevated waist circumference using population/country specific thresholds (≥ 80 cm in Caucasian women); (2) elevated triglycerides ≥ 1.7 mmol/L (≥ 150 mg/dL) or drug therapy for hypertriglyceridaemia; (3) reduced HDL-cholesterol < 1.3 mmol/L (< 50 mg/dL) in females or drug therapy for reduced HDL-C; (4) elevated blood pressure $\geq 130/85$ mmHg or drug therapy for hypertension; and (5) elevated fasting glucose ≥ 5.6 mmol/L (≥ 100 mg/dl) or drug therapy for hyperglycaemia.

Laboratory data

All subjects were studied in the morning after an overnight fast, having avoided alcohol for 48 hours. Blood was drawn and used to measure routine blood counts, lipid profiles and blood glucose. SLE subjects had serology tested, including antibodies to dsDNA (normal < 25 U), antibodies to cardiolipin (normal < 16 U; Aesku Diagnostics Wendelsheim, Germany) and C3 and C4 complement. Whether subjects had ever been positive for the above serological characteristics was also recorded. Serum insulin was measured by sensitive enzyme-linked immunosorbent assay (ELISA) (Immunodiagnostic Systems Ltd, UK), employing a monoclonal antibody to human insulin with no cross-reactivity to proinsulin. The analytical sensitivity of the assay was 1.76 mIU/L and intra and inter assay coefficients of variation were $< 3.0\%$ and $< 6.0\%$ respectively. The manufacturer's reference range in apparently normal people is 2–25 mIU/L. Insulin resistance was calculated using homeostasis model assessment which allows derivation of insulin resistance (HOMA-IR) and pancreatic beta cell function (HOMA-B) from fasting insulin/glucose pairs, using the HOMA-2 algorithm for specific insulin.¹⁹ The HOMA model for insulin metabolism has been validated against the accepted gold-standard method for measuring insulin resistance – the euglycaemic hyperinsulinaemic clamp.²⁰

Carotid imaging

As previously described, a single operator (HE) performed carotid ultrasound assessment using an ATL HDI 5000 scanner equipped with a 7-4MHz linear array transducer. The right and left common carotid

Table 1 CHD risk factors in SLE and controls

Variable	SLE n=200 ^a	Control n=100 ^a	p value
Age (years)	48(42, 56)	53(46, 59)	0.002
Post-menopausal n(%)	94(47)	59(59)	0.05
Post-menopausal if <50 yrs n(%)	18/118(15)	1/39(3)	0.03
Current smoker n(%)	40(20)	17(17)	0.8
Ex-smoker n(%)	57(28.5)	28(28)	0.8
Non-smoker n(%)	103(51.5)	55(55)	0.8
Family history of premature CHD n(%)	53(26.5)	25(25)	0.8
Systolic BP, mmHg	126(116, 140)	123.5(110, 136)	0.10
Diastolic BP, mmHg	76.5(70, 81.5)	75(68, 81)	0.22
Diagnosis of hypertension n(%)	62(31)	7(7)	<0.0001
Total cholesterol, mmol/L	5.1(4.3, 6.0)	5.7(4.9, 6.4)	0.0001
Triglycerides, mmol/L	1.0(0.8, 1.4)	1.1(0.8, 1.3)	0.90
HDL, mmol/L	1.6(1.3, 2.0)	1.7(1.4, 2.1)	0.06
Statin use	20(10)	2(2)	0.01
Fasting glucose, mmol/L	4.6(4.3, 4.9)	4.7(4.5, 5.0)	0.008

^aAll data expressed as median(IQR) unless otherwise indicated. CHD, coronary heart disease; HDL, high density lipoprotein

artery, carotid bulb and the first 1.5 cm of the internal and external carotid arteries were examined in longitudinal and cross sectional planes. Carotid plaque was defined as per the well-accepted ARIC study group definition and considered present if two of the following three conditions were met: (1) a distinct area of protrusion >50% compared with the surrounding area into the vessel lumen, (2) greater echogenicity than the adjacent boundaries and (3) intima-medial thickness of >0.15 cm.²¹

Statistical analysis

Comparison of continuous data was performed using Wilcoxon's rank sum test, and of categorical data using chi-squared test. Logistic regression was used to assess the relationship between the presence of MetS (a dichotomous outcome) and SLE factors including disease status, clinical features and therapeutic exposure. Factors associated with MetS on univariate analysis ($p < 0.10$) were entered into a multivariable logistic regression model. Logistic regression was also used to assess the relationship between carotid plaque (present or not present) and MetS and its variables. All statistical analyses were performed using STATATM 9.0.

Results

We studied 200 women with SLE and 100 healthy controls whose median (IQR) age was 48 (42, 56) years and 53 (46, 59) years respectively ($p = < 0.05$);

all subsequent analyses were therefore age-adjusted. No significant differences were seen with regards to smoking status, family history of premature CHD, triglyceride levels or blood pressure between case and controls (Table 1). The control cohort had a higher median fasting glucose (4.7 mmol/L (4.9, 5.0) vs. 4.6 (4.3, 4.9) mmol/L; $p = 0.008$) and total cholesterol (5.7 mmol/L vs. 5.1 mmol/L; $p < 0.001$), although statin use was higher in the SLE group (10% vs. 2%, $p = 0.01$).

Overall, 96% of SLE patients satisfied ≥ 4 of the 1997 revised ACR criteria. As previously described,⁴ the remaining 4% of patients satisfied 3 criteria, had a positive ANA, had additional SLE-related features and had no other medical diagnosis to account for their symptoms. Disease activity and damage indices were low at the time of assessment (median SLEDAI 2K = 1(0, 4), median SLICC = 0 (0, 1)), as would be expected from a stable outpatient population. Overall, 80% of the cohort had been exposed to corticosteroids at some point in time and, of those taking corticosteroid therapy at assessment (107 [53.5%]), the median (IQR) daily dose of prednisolone over the preceding 6 months was 6 (5, 10) mg/day. At assessment, 105 (52.5%) of lupus patients were currently receiving antimalarial therapies, although 166 (83%) of the cohort had received them at some point, and 74 (37%) were taking immunosuppressant therapy.

The SLE cohort demonstrated significant insulin resistance with a median (IQR) HOMA2-IR of 1.86 (1.47, 2.49). Those SLE subjects who met the definition for MetS had higher fasting glucose (median (IQR) 4.8 mmol/L (4.4, 5.2) vs. 4.6 (4.2, 4.8); $p = 0.01$), higher fasting insulin levels (16.7 (11.7, 20.7) u/L vs. 12.6 (9.5, 15.8) u/L; $p = 0.002$) and higher HOMA2-IR (2.26 (1.65, 2.92) vs. 1.75 (1.3, 2.25); $p = 0.001$). HOMA2-B, representing pancreatic exocrine function, did not differ according to MetS status (176 (153, 247) vs. 176 (144, 210); $p = 0.30$) in SLE patients.

The MetS was more prevalent in SLE patients (30% vs. 20%; unadjusted prevalence ratio 1.5 (0.9, 2.4)). Overall, using a logistic regression model, patients with SLE were more likely to meet the criteria for raised triglycerides, low HDL and hypertension but were no more likely to meet the threshold for raised waist circumference or impaired glucose tolerance (Table 2). No significant difference was found in measures of central obesity between SLE cases and controls: median (IQR) BMI in the SLE cohort was 25.9 (23, 30) kg/m² compared with 25.5 (23, 29) kg/m² ($p = 0.65$), and median (IQR) waist circumference was 84cm (77, 94) compared with 82 cm (76, 89) ($p = 0.35$). In those who fulfilled

the criteria for MetS there was a trend towards lower measures of central obesity in the SLE cohort compared with controls (Figure 1).

In an age-adjusted univariate analysis we assessed the strength of the relationship between SLE features and the presence of MetS. SLE patients who fulfilled the criteria for MetS were more likely to have had markers of severe disease

Table 2 Prevalence of metabolic syndrome (MetS) and its components in SLE and controls

MetS criteria	SLE cases n=200	Controls n=100	Age-adjusted OR (95%CI)
Total meeting definition	30%	20%	2.1(1.1, 3.8)
% waist circumference	64%	40%	1.3(0.8, 2.2)
% triglyceride	27%	18%	1.9 (1.02, 3.5)
% HDL	29.5%	14%	2.2 (1.3, 4.0)
% BP >130/85 mmHg	57%	40%	3.4 (1.9, 6.0)
% glucose >5.6mmol/L	7.5%	6%	1.2(0.4, 3.2)

(renal involvement, higher SLICC-DI, corticosteroid use ever and exposure to azathioprine) and longer disease duration than those who did not (Table 3). No significant association, either positive or negative, was found on univariate analysis between MetS and recent average steroid dose or use of anti-malarial therapies. In a forward step-wise regression model using significant factors found on the univariate analysis age, disease duration, corticosteroid use ever, and low C3 were all independently associated with the presence of MetS in SLE (Table 3). There was also a negative association with both haematological and neurological disorders (as per ACR criteria definition).

Carotid plaque was present in 29% of SLE cases and 22% of control subjects. In control subjects neither the presence of MetS nor any individual component was significantly associated with carotid plaque in an age-adjusted analysis. Similarly, in SLE subjects MetS was not associated with carotid plaque. However, meeting the criteria for

Figure 1 Measures of adiposity in SLE and controls. A) BMI in controls vs. SLE; B) Waist circumference (WC) in controls vs. SLE; C) BMI in controls vs. SLE (MetS only); D) WC in controls vs. SLE (MetS only).

Table 3 Significant SLE-related factors associated with MetS in univariate analysis and multivariable model.^a

Variable	Total n=200	MetS present n=60	MetS absent n=140	Age-adjusted OR (95% CI)	Multivariable model OR (95% CI)
Disease duration, yrs	8.5 (4–18)	14 (6–22)	7 (4–16)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)
Age, yrs	48 (42–58)	53 (46–59)	47 (41–54)	-	1.07 (1.03, 1.11)
Haematological disorder ever (%) ^c	163 (81.5)	44 (73)	119 (85)	0.4 (0.2, 0.8)	0.23 (0.09, 0.57)
Corticosteroid use ever (%)	160 (80)	55 (92)	105 (75)	4.0 (1.5, 11.1)	4.99 (1.59, 15.6)
Neurological disorder ever (%) ^c	14 (7)	1 (1.5)	13 (9)	0.2 (0.02, 1.3)	0.56 (0.006, 0.53)
Low C3 complement (%)	10 (5)	6 (10)	4 (3)	5.0 (1.3, 20.0)	6.76 (1.32, 34.7)
SLEDAI	1.0 (0–4)	0 (0–2)	2 (0–4)	0.9 (0.8, 1.1)	n/s
SLICC	0 (0–1)	1 (0–2)	0 (0–1)	1.3 (1.0, 1.6)	n/s
Renal disorder ever (%) ^c	32 (16)	14 (23)	18 (13)	2.4 (1.04, 5.3)	n/s
Azathioprine ever (%)	80 (40)	31 (51.6)	49 (35)	2.2 (1.1, 4.1)	n/s

^aNon-significant ($p < 0.10$) variables not shown; ^ball data expressed as median (IQR) unless otherwise indicated; ^cas per ACR criteria. MetS, metabolic syndrome.

Table 4 Association of MetS and its components with carotid plaque in SLE and controls

	SLE cases		controls	
	OR ^a	95% CI	OR ^a	95% CI
Metabolic syndrome	1.7	0.9, 3.4	2.0	0.6, 7.0
MetS WC	1.6	0.8, 3.2	1.0	0.3, 3.3
MetS HDL	1.5	0.7, 2.9	2.4	0.7, 8.7
MetS TG	2.2	1.1, 4.4	1.1	0.3, 4.7
MetS BP	2.9	1.3, 6.3	2.5	0.7, 8.2
MetS glucose	0.2	0.0, 1.3	8.5	0.9, 75.3

^aage adjusted odds ratio. HDL, high density lipoprotein; MetS, metabolic syndrome, TG, triglyceride; WC, waist circumference.

hypertriglyceridaemia and hypertension was associated with the presence of carotid plaque (OR 2.2, 95% CI (1.1, 4.4), and 2.9 (1.3, 6.3) respectively) (Table 4).

Discussion

We found a higher prevalence of MetS in women with SLE compared with healthy controls. In contrast to other studies however, the higher prevalence of MetS in SLE was not primarily driven by higher measures of central obesity^{22,23} but rather by a higher prevalence of hypertension and dyslipidaemia. In our study neither formal measures of disease activity nor damage were associated with the syndrome in a multivariable model, although surrogate measures such as low complement were. Whilst this may reflect low disease activity in a stable outpatient population of women with SLE, persistently low C3 would imply on-going disease activity despite low composite activity scores.

The observation that fulfilling either the ACR criteria for haematological or neurological manifestations was negatively associated with the MetS was initially surprising. It is likely however, that the majority of these features (such as leucopenia, lymphopenia, seizures and psychosis) would not usually be treated with high-dose corticosteroids. We noted that ever-exposure to corticosteroid therapy is associated with MetS, however average current dose used was not. Others have found similarly conflicting results^{24–27} and the ideal measure of steroid exposure to use in studies such as these is unclear. The use of steroids also of course reflects more severe disease but it is likely that the potential adverse metabolic effects of corticosteroids are balanced, at least in part, by their anti-inflammatory effects. In addition, the association with corticosteroid treatment-ever suggests some imprinting of metabolic side-effects that persist even after steroids have been withdrawn.

Our study is the first to assess the association between MetS and carotid plaque in both SLE cases and a control population. We did not demonstrate any significant association between the presence of carotid plaque and MetS in either the cases or controls. In the SLE cohort however, meeting the individual criteria for hypertriglyceridaemia and hypertension was significantly associated with the presence of carotid plaque. Recently, Mok *et al.*²⁸ described a higher coronary artery calcification score in SLE patients with MetS, compared with those without the syndrome, but found no significant differences in carotid intimal-medial thickness (IMT). Control subjects underwent no assessment for subclinical atherosclerosis. The present study has several further advantages when examining MetS in SLE. Firstly, this study has larger numbers of SLE cases and controls than previous studies.

Secondly, the study design allowed the recruitment of a relatively homogenous group of SLE patients in terms of ethnicity and gender. Finally, differences in potential confounding factors affecting the individual components of MetS related to lifestyle, education and geography between cases and controls were also minimized by our method for recruiting controls.

There are however several limitations to the present study and its analysis. Firstly, the use of a stable cohort of SLE patients with low disease activity and damage indices may reduce the ability to fully assess the impact of disease activity on MetS and carotid plaque. Secondly, we have relied on those simple measures of abdominal obesity utilized by the varied MetS definitions (waist circumference and BMI) to assess adiposity. Alternative measures such as total body densitometry have been utilized recently in small scale studies²⁹ and may reveal more subtle changes in fat mass and lean mass not detected by more clinical measures. However, their use is limited in larger scale epidemiological studies. We were also limited in data collected regarding steroid exposure, and were therefore unable to quantify cumulative steroid dose or peak doses of steroids received, which other studies have used in addition to the measures we have quoted. Finally, we were unable to perform fasting insulin measures on our control cohort, and hence are unable to comment on their levels of insulin resistance.

The higher prevalence of MetS in SLE despite similar measures of central obesity demonstrated in this study and others^{24,25,30} suggests an alternative clinical phenotype of MetS in SLE. This may reflect the effects of factors such as chronic inflammation, SLE-related disease damage and corticosteroid therapy. Others have noted that inflammatory markers relate to MetS in SLE, although there is no complete consistency between studies. For example, whilst formal measures of disease activity (such as SLEDAI) were not associated with the syndrome in the study by Sabio *et al.*,²⁴ generic measures of inflammation, such as higher ESR and CRP, were. In contrast, Negron *et al.*²⁶ found that both disease activity, as measured by SLAM-R, and higher ESR were both positively associated with MetS. We found no relationship between the SLEDAI-2K measure of disease activity but did note that low C3 complement was associated with MetS. Low complement suggests ongoing low-grade inflammation in this population. How the difference in MetS phenotype affects future CHD risk in SLE is unclear. The evidence for MetS as a tool for assessing cardiovascular risk is based on large-scale population studies of 'healthy' individuals and has

at its core central obesity as the cause of the consequent metabolic derangements.³¹ Although newer definitions of MetS are less reliant on demonstrating central obesity,^{10,32} obesity-associated insulin resistance remains central to the syndrome and its proposed pathophysiology. Many groups including our own have observed that SLE patients are significantly insulin resistant using HOMA estimates^{27,30,33} an observation supported by the present study. Therefore, it may be that insulin resistance is the final pathway and how the clinical phenotype is constituted may not change its overall consequences for CHD risk. Alternatively, increased hypertension and dyslipidaemia, and especially low HDL-cholesterol, may represent a more aggressive proatherogenic phenotype. These factors, coupled with the pro-oxidant milieu of a chronic inflammatory state, may drive accelerated atherosclerosis in SLE patients.

Whilst insulin resistance is more likely to result from chronic inflammation and/or the side effects of anti-inflammatory therapies in SLE, it is not unreasonable to assume that significant insulin resistance from any cause will have the same deleterious effects on the cardiovascular system.

In conclusion, MetS is more prevalent in SLE than in healthy controls, and this is related to age, disease duration, disease activity, and previous steroid exposure. Utilizing MetS as a method of identifying those higher risk patients may be an effective strategy in addressing CHD risk in individual patients. However, using abdominal obesity as the key prompt to screen for the syndrome is not advised and close attention to all the other factors is recommended. The long term implications of this more inflammatory and vascular MetS phenotype on future CHD events requires prospective study.

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Conflict of interest

none declared.

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