Hyperinsulinemia, Insulin Resistance, and Circulating Oxidized Low Density Lipoprotein in Women with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Women with systemic lupus erythematosus (SLE) have increased risk of coronary heart disease (CHD) that is not fully explained by the classic CHD risk factors. Insulin resistance is an established risk factor for CHD in the general population. We compared insulin secretion and sensitivity in patients with SLE and healthy controls, and assessed the prevalence of the metabolic syndrome in women with SLE and its relation to circulating oxidized low density lipoprotein (ox-LDL).

Methods. Fasting insulin, glucose, and lipid profiles were measured in nondiabetic women with SLE (≥ 4 revised 1997 criteria) not undergoing antimalarial therapy (n = 44), and in age matched controls recruited from the hospital staff and the local community (n = 45). Using the Homeostatic Model Assessment equations, insulin sensitivity (HOMA-S) and pancreatic beta cell function (HOMA-B) were calculated from fasting insulin and glucose. The metabolic syndrome, defined according to the Adult Treatment Panel (ATP III) criteria, was determined in a consecutive series of 61 women with SLE.

Results. Patients with SLE had significantly higher fasting insulin [median (range) 10 (2.8–38) vs 6.6 (3.1–26) mU/l; $p < 0.01$], higher pancreatic beta cell function (HOMA-B) [165 (54–1567) vs 111 (28–653); $p < 0.01$], and lower insulin sensitivity (HOMA-S) [0.46 (0.09–1.9) vs 0.73 (0.16–1.3); $p < 0.01$]. SLE patients also had significantly higher triglycerides ($p < 0.01$) and lower high density lipoprotein cholesterol ($p < 0.01$) than controls. HOMA-S did not correlate with disease activity or steroid therapy, but was associated with components of the insulin resistance syndrome. HOMA-S showed a significant negative correlation with levels of ox-LDL in patients, but not in controls. Eleven (18%) patients had the metabolic syndrome. Again, this was not related to current steroid therapy. SLE patients with the metabolic syndrome had no difference in LDL, but had significantly higher levels of ox-LDL.

Conclusion. Nondiabetic patients with SLE have evidence of significant decrease in sensitivity to insulin, and overall this population has a high prevalence of the metabolic syndrome (18%). Insulin resistance in the context of SLE was not strongly related to current or recent steroid therapy; it was, however, associated with higher levels of ox-LDL. Insulin resistance may therefore represent an additional CHD risk factor in patients with SLE. (J Rheumatol 2006;33:50–6)

Key Indexing Terms:
HYPERINSULINEMIA INSULIN RESISTANCE WOMEN
OXIDIZED LOW DENSITY LIPOPROTEIN SYSTEMIC LUPUS ERYTHEMATOSUS

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Accelerated atherosclerosis and premature coronary heart disease (CHD) are now recognized to be important causes of mortality and morbidity in patients with systemic lupus erythematosus (SLE)[1]. Women with SLE have a significantly higher risk of developing myocardial infarction than women in the general population[2]. Established Framingham risk factors influence the development of atherosclerosis in this setting[3,4]. However, even after adjusting for the presence of Framingham risk factors, Esdaile, *et al*[5] noted that there was still a 7 to 17-fold increased risk of cardiovascular events in patients with SLE. Such observations suggest that patients with SLE possess additional risks for the development of CHD. These risk factors may be related to additional metabolic changes and/or immune-inflammatory factors.

In recent years, insulin resistance has been investigated

as a potential CHD risk factor in the general population. Insulin resistance is strongly associated with the presence of type II diabetes mellitus and can be defined as the reduced ability of insulin to stimulate glucose uptake in skeletal muscle and fat cells and to inhibit lipolysis in adipose tissue[6]. The metabolic state of insulin resistance is associated with a clustering of CHD risk factors, including increased waist:hip ratio, raised triglycerides, and hypertension, as well as reduced high density lipoprotein cholesterol (HDL). This cluster is associated with an increased CHD risk, particularly in women[7]. As such, the metabolic syndrome has been recognized in the Adult Treatment Panel (ATP) III Guidelines of The National Cholesterol Education Program (2001)[8] as important in identifying people at CHD risk who need more intensive risk factor management. The exact mechanism by which hyperinsulinemia acts as a CHD risk factor remains controversial, but some studies report an independent effect of insulin on the development of atherosclerosis[9].

Cross-sectional studies of SLE cohorts have found that diabetes mellitus occurs more frequently than expected. Petri *et al*[10] found that 7% of patients with SLE had diabetes mellitus and 10% had glucose intolerance[11]. More recently, a cohort control study found diabetes to be significantly more common in patients with lupus than in the general population[12]. Our hypothesis was therefore that patients with SLE have reduced sensitivity to insulin. The specific aims of our study were to compare insulin secretion and sensitivity in patients with SLE and healthy controls. We also assessed the prevalence of the "metabolic syndrome" in a larger cross-sectional cohort of women with SLE.

MATERIALS AND METHODS

Patients and controls. We recruited women with SLE (≥ 4 revised 1997 American College of Rheumatology criteria[13]) from the Lupus and Connective Tissue Disease Clinic at Manchester Royal Infirmary. For the comparative study of lupus patients and healthy controls, we excluded patients who satisfied the World Health Organization criteria for diagnosis of diabetes mellitus and also those taking antimalarial drugs (chloroquine phosphate or hydroxychloroquine sulfate). Antimalarial drugs have several effects on insulin metabolism. Principally, they prolong the half-life of the active insulin-receptor complex through inhibition of insulin dissociation from its receptor[14]. As a result, antimalarials invalidate the mathematical modeling used to calculate insulin sensitivity and beta cell secretory function. Hospital staff and community controls with no history of diabetes mellitus, recruited from the local community, were age-matched to patients in 5-year age bands. All subjects gave written consent and the study was approved by the Central Manchester Local Research Ethical Committee.

All patients and controls were studied following an overnight fast and avoidance of alcohol for 48 h. Patients had a clinical assessment of standard CHD risk factors as well as anthropomorphic measurements including body mass index (BMI), waist:hip ratio, hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg or undergoing antihypertensive therapy). Current drug therapy was also noted and inflammatory disease activity was assessed using the SLE Disease Activity Index (SLEDAI)[15].

We used the definition employed by the Adult Treatment Panel (ATP III) to define the presence of the metabolic syndrome in a larger cross-sectional cohort of unselected patients with SLE. The metabolic syndrome was said to be present if patients had 3 or more of the following: waist circumference > 88 cm; serum triglycerides ≥ 1.69 mmol/l; HDL < 1.29 mmol/l; elevated blood pressure of ≥ 130 mm Hg systolic, ≥ 85 mm Hg diastolic, or on antihypertensive therapy; plasma glucose ≥ 6.1 mmol/l.

Laboratory methods. Blood samples were drawn between 9 and 11 A.M. after patients and controls had fasted from 10 P.M. the previous day and plasma and serum separated prior to laboratory analysis. Fasting plasma glucose was measured in the hospital laboratory on the day of blood collection using the glucose oxidase method.

Measurement of plasma insulin. Insulin was measured by sensitive delayed addition radioimmunoassay, a specifically modified method to enhance assay sensitivity within the adult normal fasting range. This assay has a lower limit of detection of 0.38 mU/l. Using this assay, the median fasting plasma insulin concentration in a reference range of 191 healthy hospital employees was 4.8 mU/l with an interquartile range of 3.4–6.4 mU/l[16].

Homeostasis Model Assessment. Homeostasis Model Assessment (HOMA) is an arithmetic way of deriving indices of pancreatic endocrine function (beta cell function, HOMA-B) and peripheral tissue insulin sensitivity (HOMA-S) from fasting plasma samples[17]. This model assumes that plasma glucose and insulin in the fasting state is controlled by a feedback loop between the pancreas, liver, and insulin-sensitive and insulin-insensitive peripheral tissues. HOMA correlates well with and is validated against the gold standard methods of assessment of these functions, such as the euglycemic hyperinsulinemic clamp[18,19].

HOMA-S and HOMA-B are derived using the formulae:

$$\text{HOMA-S} = 22.5/[\text{insulin (mU/l)} \times \text{glucose (mmol/l)}]$$

$$\text{HOMA-B} = [20 \times \text{insulin (mU/l)}]/[\text{glucose (mmol/l)} - 3.5)]$$

In an "ideal" reference population of young, healthy subjects HOMA-B and HOMA-S are 100% and 1 (arbitrary units), respectively.

Lipoprotein analysis. Ultracentrifugation was used to remove VLDL from the plasma. HDL was then determined following precipitation of LDL from the resulting infranatant by heparin/Mn^{2+} sulfate. Total serum cholesterol, HDL, and infranatant cholesterol were determined by the cholesterol esterase/peroxidase (CHOD-PAP) method. LDL was calculated as the difference between infranatant cholesterol and HDL[20]. Serum triglycerides were determined by the GPO-PAP method. Oxidized LDL (ox-LDL) level in mU/l was assayed by a 2-site ELISA (sandwich technique), in which 2 monoclonal antibodies are directed against separate antigenic sites on the apolipoprotein molecule on LDL. Ox-LDL ELISA kits were supplied by Mercodia AB, Uppsala, Sweden.

Carotid artery assessment. Within 1 month of study, 40 patients had a carotid artery scan to determine carotid intima media thickness (IMT) and presence of carotid plaque. IMT measurement was taken in the proximal part of the common carotid arteries (CCA) 1 cm proximal to the carotid bulb as the maximum distance between the intima-lumen and adventitia-media interfaces in areas without carotid plaque[21]. IMT was determined as the average of 6 measurements, 3 each from the left and right CCA. Presence or absence of carotid plaque was defined using the criteria described by Li, *et al*[22].

Statistical analysis. Version 10.1 of the SPSS statistical package was used for the analyses. Data are presented as medians and ranges. Differences between numeric variables were tested for significance using the Mann-Whitney U test. Correlations between variables were tested using Spearman's rank analysis. Significance level was set at probability value ≤ 0.05. Chi-square and Fisher's exact tests were used for comparison of categorical variables or percentages.

RESULTS

Insulin sensitivity in SLE patients and controls. We studied 44 Caucasian women with SLE and 45 healthy controls.

Their median (range) age was 50.5 (26–67) and 48 (28–62) years, respectively. SLE patients had a median (range) disease duration of 12 (1–35) years. The overall disease activity was low, with a median (range) SLEDAI score of 2 (0–8). Fourteen (32%) patients were currently taking steroid therapy. Patients with SLE had higher serum triglycerides ($p = 0.02$) and lower HDL ($p < 0.01$) than controls (Table 1). They were also more likely to be hypertensive ($p = 0.01$). While there was no difference in BMI or waist circumference, waist:hip ratio was significantly higher in SLE patients ($p < 0.01$). All patients and controls had a fasting glucose < 7.0 mmol/l. Fasting plasma insulin levels were higher ($p < 0.01$) and insulin sensitivity (HOMA-S) was lower ($p < 0.01$) in SLE patients compared to controls (Table 1, Figure 1). The beta cell secretory function (HOMA-B) was also higher in SLE patients ($p < 0.01$; Table 1).

Within the group of SLE patients, the HOMA-S showed no correlation with disease activity as measured by the SLEDAI. HOMA-S was lower in patients taking steroids (Figure 2), but this did not reach statistical significance, and there was only a weak correlation between HOMA-S and current steroid dose and average daily dose of steroids over the previous 6 months (Table 2). There was no significant difference in HOMA-S between patients positive (n = 16) or negative for anticardiolipin antibodies [0.45 (0.9–1.0) vs 0.46 (0.14–1.9); p nonsignificant]. Compared to controls, patients not taking steroids still had significantly lower HOMA-S ($p = 0.021$; Figure 2). They also had significantly higher fasting insulin and HOMA-B (data on file). In both patients and controls, HOMA-S correlated significantly with BMI ($p < 0.01$) and waist circumference ($p < 0.01$); and more strongly with waist:hip ratio in patients ($p < 0.01$) than controls ($p = 0.04$). HOMA-S was also correlated with triglycerides and HDL in the patients and controls (Table 2). While there was a strong negative correlation of HOMA-S and both LDL ($p = 0.01$) and ox-LDL ($p < 0.01$) in patients, this was not seen in controls (Table 2). With regard to subclinical atherosclerosis, HOMA-S did not differ in those with or without plaque [0.55 (0.24–0.84) vs 0.46 (0.09–1.5); p nonsignificant]. Similarly, there was no significant correlation between carotid IMT and HOMA-S ($r = 0.16$, $p = 0.33$).

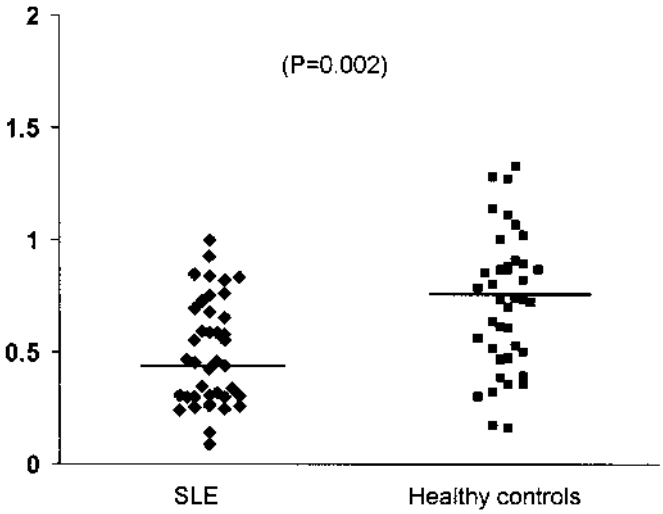

Figure 1. Insulin sensitivity (HOMA-S) in SLE patients and healthy controls.

Metabolic syndrome in SLE patients. Of the 61 consecutive women with SLE, 3 (5%) were known to have diabetes mellitus. Fifty-one (84%) were white Caucasians, 2 South Asian, 2 black Caribbean, 2 black African, 2 Chinese, one Iranian, and one Iraqi. The median (range) age and disease duration were 48 (21–73) and 11 (1–32) years, respectively. Twenty-nine patients were on antimalarial therapy and 33 on steroid therapy. Eleven (18%) patients had ≥ 3 of the metabolic syndrome criteria. The frequency of each measure contributing to the syndrome is given in Figure 3. As shown,

Table 1. Comparison of metabolic risk factors and insulin measures between SLE patients and healthy controls. HOMA-S and HOMA-B represent insulin sensitivity and beta cell secretory function, respectively.

	SLE*, n = 44	Controls*, n = 45	p
Age, yrs	50.5 (26–67)	48 (25–62)	NS
BMI, kg/m^2	26.6 (18.6–37.4)	24.8 (17–36.2)	NS
Waist, cm	82.5 (66–107)	80 (58–107)	NS
Waist:hip ratio	0.82 (0.69–0.96)	0.77 (0.68–0.89)	< 0.01
Total cholesterol, mmol/l	5.4 (3.3–8.7)	5.0 (2.6–7.2)	NS
HDL, mmol/l	1.5 (0.8–2.7)	1.7 (1.0–3.0)	< 0.01
Triglycerides, mmol/l	1.2 (0.4–4.1)	0.9 (0.4–3.1)	0.02
Hypertension (%)	15/42 (36.4)	3/32 (9.4)	0.01
Fasting glucose, mmol/l	4.7 (3.8–6.7)	4.8 (3.8–6.1)	0.11
Insulin, mU/l	10.0 (2.8–38)	6.6 (3.1–26.4)	< 0.01
HOMA-S	0.46 (0.09–1.9)	0.73 (0.16–1.3)	< 0.01
HOMA-B	165 (54.3–1567)	111 (28–653)	< 0.01

* Median (range) unless otherwise stated. HDL: high density lipoprotein cholesterol, BMI: body mass index.

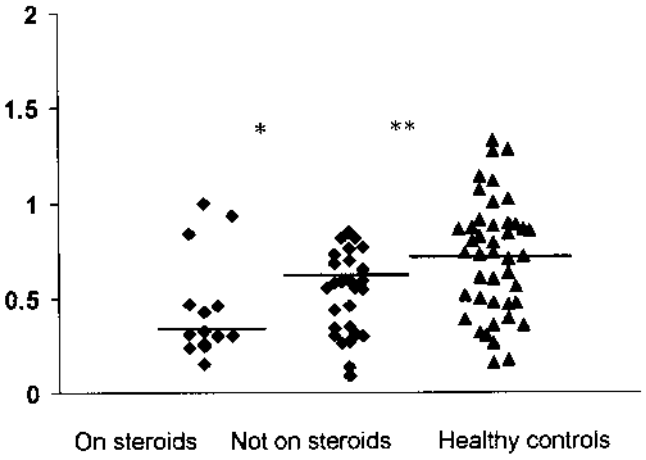

Figure 2. HOMA-S in SLE patients with and without steroid therapy compared to healthy controls. *Patients not on steroid vs patients on steroid (p = 0.163). **Patients not on steroid vs healthy controls (p = 0.02).

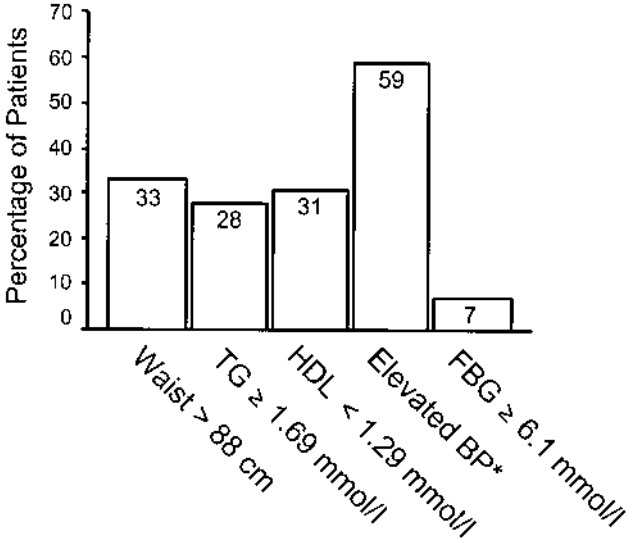

Figure 3. Frequency of each criterion of metabolic syndrome in 61 patients with SLE. *See Materials and Methods for ATP III definition of elevated blood pressure. TG: triglycerides, HDL: high density lipoprotein cholesterol, FBG: fasting blood glucose.

elevated blood pressure (including patients on antihypertensive therapy) was the most frequent feature, being present in 36 (59%) of all patients with SLE. Comparing those with and without the syndrome (Table 3), both groups were of similar age and disease duration. As expected, the fasting insulin levels were higher in those with the metabolic syndrome. Although there was no difference on LDL levels, those with the metabolic syndrome had significantly higher ox-LDL concentrations. Comparing those with and without the metabolic syndrome, there was no difference in numbers of patients currently taking steroid or antimalarial therapy. In addition, there was no difference in the current steroid dose or the mean daily dose over the past 6 months between those with and those without the syndrome. Those with the metabolic syndrome did not differ with respect to levels of clinical disease activity or presence of antiphospholipid antibodies. Eleven (18%) patients had carotid plaque. There was no significant difference between those with and without the metabolic syndrome in IMT [0.05 (0.04–0.10) vs 0.05 (0.03–0.08) cm; p nonsignificant] or in numbers with carotid plaque [1/11 (8.3%) vs 10/50 (20%); p nonsignificant].

DISCUSSION

In this study we found evidence of hyperinsulinemia and reduced insulin sensitivity in a cohort of patients with SLE.

Table 2. Spearman rank correlations of HOMA-S in SLE patients and healthy controls.

	SLE,		Controls,	
	r_s	p	r_s	p
Age	–0.13	NS	–0.16	NS
Body mass index	–0.44	< 0.01	–0.50	< 0.01
Waist circumference	–0.44	< 0.01	–0.58	< 0.01
Waist:hip ratio	–0.41	< 0.01	–0.37	0.04
Systolic BP	–0.14	NS	–0.27	NS
Diastolic BP	–0.35	0.02	–0.32	0.08
Fasting glucose	–0.25	0.11	–0.33	0.03
Triglycerides	–0.56	< 0.01	–0.43	0.02
HDL	0.34	0.03	0.38	0.04
LDL	–0.40	0.01	–0.19	NS
Ox-LDL	–0.57	< 0.01	–0.06	NS
SLEDAI	0.15	NS	—	—
Current steroid dose	–0.19	NS	—	—
Average daily steroid dose in the last 6 mo	–0.24	NS	—	—
Duration of steroid therapy	–0.10	NS	—	—

BP: blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, Ox-LDL: oxidized LDL, SLEDAI: SLE Disease Activity Index, NS: nonsignificant.

Table 3. Comparison of SLE patients with and without the metabolic syndrome.

	Metabolic Syndrome, n = 11*	No Metabolic Syndrome, n = 50*	p
Age, yrs	46 (26–73)	49.5 (21–67)	NS
BMI	29 (24–34)	25 (19–42)	< 0.01
Disease duration, yrs	6 (1–29)	12 (1–32)	NS
Fasting glucose, mmol/l	5.9 (3.8–7.9)	4.5 (3.6–10.9)	0.03
Fasting insulin, mU/l	18.9 (4.5–38)	10 (2.8–40.7)	0.01
LDL, mmol/l	3.1 (1.4–4.3)	2.7 (0.3–5.0)	NS
Ox-LDL mU/l	45.7 (18–61)	31.7 (13–77)	0.02
Current steroid therapy, n (%)	4 (36.4)	29 (58)	NS
Current steroid dose, mg/day	0.3 (0–30)	4.0 (0–30)	NS
Average daily steroid dose in the last 6 months, mg/day	0.7 (0–10)	5.0 (0–20)	NS
Duration of steroid therapy, mo	37 (0–372)	39 (0–264)	NS
Antimalarial therapy, n (%)	4 (36.4)	25 (50)	NS
SLEDAI	2 (0–12)	2.0 (0–8)	NS

* Median (range) unless stated otherwise. LDL: low density lipoprotein, Ox-LDL: oxidized LDL, BMI: body mass index, SLEDAI: SLE Disease Activity Index, NS: nonsignificant.

We also found that 18% of unselected patients with SLE have metabolic syndrome. As far as we are aware, this is the first systematic study of insulin measures in adults with SLE. Others have included patients with SLE as part of broader studies of insulin handling in inflammatory rheumatic diseases[23]. A recent study of pediatric and adolescent patients with SLE found significantly higher fasting insulin in patients compared to controls[24]. The median HOMA-S in our patient group was similar to the degree of insulin sensitivity seen in newly diagnosed type II diabetics and in women with polycystic ovary syndrome[25]. Patients with lupus, however, maintain their euglycemic state by significantly increasing insulin secretion from pancreatic beta cells. In keeping with insulin resistance being part of the overall metabolic syndrome, we also found strong negative correlations between HOMA-S and several established risk factors within this "insulin resistance cluster," i.e., BMI, waist circumference, triglycerides, and HDL. These associations were also observed in the control population. High triglycerides and low HDL are the most frequently observed lipid profile abnormalities in SLE, which are aggravated by disease activity[26,27] and resemble the atherogenic dyslipidemia (high triglycerides, low HDL, and increased small dense LDL) associated with diabetes and insulin resistance states[28]. High triglyceride levels have been shown to enhance the formation of smaller dense particles of LDL[29]. Of particular interest was the observation that insulin levels correlated with ox-LDL in the patient group but not in the control group. Some investigators have noted that patients with SLE have an excess of small dense LDL particles, which are more susceptible to oxidation[24,30]; this may partly explain the association we found. Other pro-oxidant pathways have also been suggested in SLE patients, such as low paraoxonase-1 activity[31]. In addition, hyperinsulinemia may itself be associated with increased oxidant stress. In patients with SLE, therefore, the presence of insulin resistance may be in part a cause and/or a consequence of these pro-oxidant pathways. We did not find an association between HOMA-S and markers of subclinical atherosclerosis, specifically carotid plaque and IMT. This could be related, first, to the small number of patients, which obviously reduces the power to detect a difference; and second, insulin resistance in SLE could be associated more with clinical events rather than subclinical atherosclerosis, as it is associated with increased procoagulant and proinflammatory factors. Third, as it was cross-sectional, this study may not detect a true association, and a prospective study is needed to address this question.

In the second part of the study we confirmed the presence of the metabolic syndrome in 18% of our cohort. These patients had higher fasting insulin levels than those without the syndrome. In our control group, which was not strictly matched for age to the whole SLE group, we found only one of 38 (2.5%) to have the metabolic syndrome. A larger study is needed to confirm this. However, our findings suggest that both insulin resistance and the metabolic syndrome occur more frequently in patients with SLE. These findings are of importance in view of the major impact that insulin resistance and the associated metabolic syndrome can have on cardiovascular risk. That insulin resistance may be a more significant risk factor in women[7] may also partly explain the loss of protection against CHD observed in patients with SLE[2].

With regard to factors that may promote the development of reduced insulin sensitivity in lupus, we found only a modest association with corticosteroids in this context. Although patients taking steroids tended to have lower insulin sensitivity, patients not on steroids still had significantly decreased insulin sensitivity compared with controls. Also, there was only a weak association between HOMA-S and

current steroid dose or steroid dose in the past 6 months. In our larger group of patients with metabolic syndrome, again steroid therapy did not appear to be a significant factor. Indeed, patients with the metabolic syndrome appeared, if anything, to be exposed to less steroids. These findings are supported by Posadas-Romero, *et al*[24], who noted that only 15.6% of the variance in fasting insulin levels was explained by prednisolone dose in their SLE population. It is difficult to conceive that glucocorticoids are not important in this regard and it therefore may be that interindividual variability in the metabolic response to a particular steroid dose is more important in determining steroid side effects; this would not be fully accounted for in a cross-sectional study such as this. Also, since steroids are employed for their anti-inflammatory properties in SLE they may in part be beneficial. Further study of these interactions is under way.

Several limitations to this study must be addressed. First, we were unable to include patients taking antimalarial drugs in the first part of the study. As we have noted, antimalarial drugs have been found to inhibit insulin dissociation from its receptor, resulting in an increased half-life of the active insulin-receptor complex[14]. Antimalarials therefore may be beneficial in this context, and Petri, *et al*[11] have noted lower fasting blood glucose concentrations in patients taking antimalarials. The only reliable way to study the effect of antimalarials on peripheral insulin resistance would be with formal clamping experiments, which were beyond the scope of this study. Second, we were unable to fully evaluate other factors known to be associated with the metabolic syndrome in the general population, in particular disturbances of the coagulation system. Patients with insulin resistance are more likely to have elevated levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1). Raised levels of fibrinogen and PAI-1 have been found in patients with SLE[32,33]. Clearly, in a condition where thrombotic risk is already increased by the presence of antiphospholipid antibodies, this interaction with other procoagulant pathways may have a significant effect on subsequent risk of coronary events and requires evaluation. The third limitation is that we have no data on how this cluster of risk factors or insulin resistance alone may influence atherogenesis and the onset of coronary heart disease in this context. Such a study would require a prospective evaluation of a large cohort and clearly needs to be undertaken, especially in light of the association with oxidized LDL levels, which have been associated with the development of atheroma in SLE[34], and also the association in the general population of ox-LDL with the components of the metabolic syndrome, LDL particle size, and with increased risk of CHD[35,36].

We found that nondiabetic patients with SLE have evidence of significantly reduced sensitivity to insulin, and overall, this population has a high prevalence of the metabolic syndrome (18%). Insulin resistance in the context of SLE was not strongly related to current or recent steroid therapy. Given that insulin resistance and many of its associated metabolic changes are not reflected in the standard Framingham risk factor profile, insulin resistance may represent a significant additional risk factor in this predominantly female population. Further studies are under way to prospectively evaluate the effect of insulin resistance within lupus, and this may represent an important avenue for interventions in this patient population.

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