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## Original article

## Lower vitamin D is associated with metabolic syndrome and insulin resistance in systemic lupus: data from an international inception cohort

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## Abstract

**Objectives.** Vitamin D (25(OH)D) deficiency and metabolic syndrome (MetS) may both contribute to increased cardiovascular risk in SLE. We aimed to examine the association of demographic factors, SLE phenotype, therapy and vitamin D levels with MetS and insulin resistance.

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**Methods.** The Systemic Lupus International Collaborating Clinics (SLICC) enrolled patients recently diagnosed with SLE (<15 months) from 33 centres across 11 countries from 2000. Clinical, laboratory and therapeutic data were collected. Vitamin D level was defined according to tertiles based on distribution across this cohort, which were set at T1 (10–36 nmol/l), T2 (37–60 nmol/l) and T3 (61–174 nmol/l). MetS was defined according to the 2009 consensus statement from the International Diabetes Federation. Insulin resistance was determined using the HOMA-IR model. Linear and logistic regressions were used to assess the association of variables with vitamin D levels.

**Results.** Of the 1847 patients, 1163 (63%) had vitamin D measured and 398 (34.2%) subjects were in the lowest 25(OH)D tertile. MetS was present in 286 of 860 (33%) patients whose status could be determined. Patients with lower 25(OH)D were more likely to have MetS and higher HOMA-IR. The MetS components, hypertension, hypertriglyceridemia and decreased high-density lipoprotein (HDL) were all significantly associated with lower 25(OH)D. Increased average glucocorticoid exposure was associated with higher insulin resistance.

**Conclusions.** MetS and insulin resistance are associated with lower vitamin D in patients with SLE. Further studies could determine whether vitamin D repletion confers better control of these cardiovascular risk factors and improve long-term outcomes in SLE.

**Key words:** systemic lupus erythematosus, vitamin D, cardiovascular disease, epidemiology

#### Rheumatology key messages

- In patients newly diagnosed with SLE, lower 25(OH)D was associated with MetS and insulin resistance.
- Significant associations of MetS and lower 25(OH)D despite adjustment of patient factors indicates cardiovascular risk.
- Further trials exploring vitamin D supplementation are needed to optimise cardiometabolic outcomes in SLE.

## Introduction

25-hydroxyvitamin D (25(OH)D) deficiency is associated with an increased prevalence of cardiovascular disease (CVD) in the general population [1, 2]. Patients with SLE have an excess cardiovascular risk, up to 50 times that seen in comparator populations [3–6]. This increased incidence of CVD cannot be attributed to traditional cardiovascular risk factors alone [7], and therefore it is likely that other variables may have a contributing role.

Vitamin D is traditionally known for its primary function in calcium homeostasis, and has an emerging role in modulating immune responses and in autoimmune disease [8]. Vitamin D receptor expression has been described in innate and adaptive immune cells [9, 10], and it has been shown that a vitamin D-deficient diet increased disease activity and CVD features in animal models of SLE [11]. Indeed, vitamin D deficiency is more common in patients with SLE compared with age-matched controls [12–14]. A previous study demonstrated a significant association between patients with low 25(OH)D and cardiovascular risk, which was no longer significant after adjusting for BMI [14]. In the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort, our previous analysis involving 890 patients showed an association between lower vitamin D levels and an increased likelihood of having hypertension, hyperlipidaemia, higher CRP and disease activity that remained significant despite adjusting for BMI [12].

While vitamin D deficiency has been associated with classic cardiovascular risk factors in SLE, much less is known about its relationship with metabolic syndrome (MetS) [15]. A number of metabolic abnormalities constitute MetS; not all of which are assessed in routine cardiovascular screening tools. MetS is recognised to reflect an increased risk of atherosclerosis and type II diabetes mellitus and is also associated with increased insulin resistance [16]. Compared with the general population, patients with SLE are more likely to fulfil MetS criteria [17–19]. In addition to being more prevalent in SLE (38%), MetS was also independently associated with increased baseline renal disease, pre-existing organ damage, higher disease activity, older age and Hispanic or Black race/ethnicity [20].

Lower 25(OH)D levels have also previously been associated with increased insulin resistance in non-diabetic patients with SLE [13]. The aim of our study was to extend the findings of our previous work [12] and to determine the association between vitamin D levels and MetS in a large international multicentre SLE inception cohort.

## Methods

### SLICC inception cohort

Between 1999 and 2011, 1847 patients were recruited into the inception cohort from 33 centres across North

America, Europe and Asia. Patients included in this cross-sectional study were recruited within 15 months of confirming  $\geq 4$  SLE ACR 1997 classification criteria [20, 21]. Disease activity was quantified by the SLE Disease Activity Index-2000 (SLEDAI-2K) [22]. Laboratory tests (fasting or non-fasting) for clinical markers of disease activity and CVD risk factors, and to define MetS were performed at each site. All patients provided informed consent. This study was approved by the University Health Network Research Institute research ethics committee, Toronto, Canada and by the Institutional Research Ethics Boards of all participating centres in accordance with the Declaration of Helsinki's guidelines for research in humans.

### Vitamin D measurement

Serum 25(OH)D was measured by LIAISON<sup>®</sup> Vitamin D TOTAL assay (310600, Diasorin, Toronto, Canada) through the University Health Network Laboratory Medicine Program. The intraassay coefficient of variation was 5.4% and the inter-assay coefficient of variation was 10.6%.

### Traditional CVD risk factors and definition of MetS

Variables for traditional CVD risk factors were collected, including hypertension, BMI, hypercholesterolemia, diabetes mellitus, smoking and post-menopausal status. Hypertension was defined as an elevated blood pressure of  $\geq 140/90$  mm, or currently being prescribed anti-hypertensive medication. Diabetes mellitus was defined as fasting glucose  $\geq 7.0$  mmol/l or a documented diagnosis of diabetes. Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) method [23] in patients who had a fasting sample for glucose and insulin measurement. Values of HOMA-IR above 1.0 denote increasing insulin resistance.

MetS was defined using the 2009 definition in the joint interim statement from the International Diabetes Federation Task Force on Epidemiology and Prevention and interested partners [15]. This harmonizing statement for a MetS diagnosis requires three or more of the following five criteria to be present: (i) elevated waist circumference (MetS WC) using gender and ethnicity-specific thresholds; (ii) elevated serum triglyceride (MetS TG) of  $\geq 1.7$  mmol/l or being on lipid-lowering medication; (iii) reduced high-density lipoprotein (HDL) (MetS HDL) of  $< 1.3$  mmol/l in women and  $< 1.0$  mmol/l in men; (iv) elevated BP (MetS BP) of  $\geq 130/85$  mm or receiving anti-hypertensive medication; and (v) elevated fasting glucose (MetS Glu) of  $\geq 5.6$  mmol/l or being prescribed medication for hyperglycaemia. In patients with missing data on specific MetS criteria, those who fulfilled three or more criteria from the data available could still be classified as MetS. For those in whom three or more criteria were not fulfilled from the data available, they were still able to be classified as not having MetS. In other situations, patients remained unclassified.

### Statistical analysis

Potential variables that may influence serum 25(OH)D and the prevalence of MetS in SLE were defined *a priori* including: age, gender, race/ethnicity (Caucasian, Hispanic, Asian, Black and other), location (Canada, USA, Mexico, Europe, South Korea), disease activity (SLEDAI-2K), cardiovascular risk factors, a MetS diagnosis and SLE-related medication (anti-malarials and glucocorticoids). To adjust for ultraviolet exposure, latitude was used as an approximation of the centre location [24], which were all located in the northern hemisphere. Patients were classified as 'low latitude', 'middle latitude' and 'high latitude' based on their centre being located between 20° and 34° north (°N), 35° and 45°N and north of 45°N respectively. Continuous data were compared using Wilcoxon rank sum-test and categorical data using the  $\chi^2$  test. Due to varied definitions of cut-off values for 25(OH)D levels in the general population, our cohort was categorised into tertiles, defined as T1 (10–36 nmol/l), T2 (37–60 nmol/l) and T3 (61–174 nmol/l), which were used to determine the association between vitamin D levels and cardiovascular and SLE risk factors. Linear and logistic regression models were used to investigate associations between 25(OH)D treated as a continuous variable and predefined variables related to SLE disease phenotype and MetS, and traditional cardiovascular risk factor. For linear regression, some variables were log-transformed to satisfy assumptions of normality and 25(OH)D divided by a constant to produce interpretable beta-coefficients. Logistic regression was used to analyse categorical variables. Receiver operating characteristic (ROC) and area under the ROC curve (AUC) were used to assess the probability of patients having MetS and to assess the role of 25(OH)D in this model. Statistical analyses were performed using StataMP-64 v13.0 (College Station, TX: StataCorp LLC, USA).

## Results

### Patients

Serum 25(OH)D was measured at enrolment in 1163 patients from a cohort of 1847 (63%). Patient characteristics are summarized in Table 1. The majority of the cohort were female (1034/1163, 88.9%) with a median (IQR) age of 33.1 (24.3, 43.6) years, disease duration was 21.7 (9.1, 39.9) weeks and 623/1163 (53.6%) were Caucasian. The group who did not have a sample to measure vitamin D status had similar demographics and disease activity but were different in ethnicity and country of residence compared with the remaining cohort, and had a higher average daily oral glucocorticoid exposure, total cholesterol and serum triglyceride (Supplementary Table S1, available at *Rheumatology* online).

### Vitamin D status

The median (IQR) 25(OH)D level in the cohort of 1163 patients was 48 (30, 66) nmol/l, in which 398 (34.2%)

**TABLE 1** Demographic and baseline disease characterization of patients the SLICC population

Characteristics ( <i>n</i> ≥ 90% cohort unless stated otherwise)	<i>n</i> (%) / median (IQR)
Age (years)	33.1 (24.3, 43.6)
Gender	
Female	1034 (88.9)
Male	129 (11.1)
Ethnicity	
Caucasian	623 (53.6)
Hispanic	47 (4.0)
Asian	243 (20.9)
Black	202 (17.4)
Other	48 (4.1)
Country/continent	
Canada	346 (29.8)
USA	312 (26.8)
Mexico	10 (0.9)
Europe	339 (29.1)
Asia	156 (13.4)
Latitude (°N)	
20–34°N	116
34–45°N	625
North of 45°N	422
25(OH)D (nmol/l)	
Serum 25(OH)D levels (nmol/l)	48 (30, 66)
CVD risk factors	
Systolic BP (mm Hg)	120 (110, 130)
Diastolic BP (mm Hg)	75 (70, 80)
BMI (kg/m <sup>2</sup> )	23.7 (21.1, 27.7)
Waist circumference (cm), <i>n</i> = 987	80 (73, 90)
Smoking status	173 (14.9)
Post-menopausal, <sup>a</sup> <i>n</i> = 1034	104 (10.1)
Total cholesterol (mmol/l)	4.6 (3.9, 5.5)
Serum triglyceride (mmol/l), <i>n</i> = 987	1.3 (1.0, 2.0)
HDL-cholesterol (mmol/l), <i>n</i> = 634	1.3 (1.0, 1.7)
LDL-cholesterol (mmol/l), <i>n</i> = 531	2.5 (2.0, 3.1)
Fasting glucose (mmol/l), <i>n</i> = 985	4.7 (4.3, 5.3)
Measures based on fasting insulin	
Fasting insulin (uIU/ml), <i>n</i> = 413	3.0 (1.9, 5.4)
HOMA-IR, <i>n</i> = 396	0.7 (0.4, 1.3)
SLE-related characteristics	
Disease duration (wks)	21.7 (9.1, 39.9)
SLEDAI-2K score	4 (2, 8)
Anti-dsDNA positive	450 (42.0)
Low C3/C4 <sup>b</sup>	440 (40.6)
CRP (mg/l), <i>n</i> = 868	3.0 (1.9, 6.3)
Creatinine (umol/l), <i>n</i> = 746	69.0 (61.0, 79.6)
Active renal disease <sup>c</sup>	231 (19.9)
Receiving oral glucocorticoids	801 (68.9)
Average glucocorticoid dose (mg/day)	10 (0, 25)
Anti-malarials	828 (71.3)
Immunosuppressants	452 (38.9)
Cardiovascular-related medications ( <i>n</i> , %)	
Anti-hypertensive medication	322 (27.7)
Lipid-lowering medication	112 (9.6)

<sup>a</sup>Percentage of women. <sup>b</sup>Decrease in CH50, C3 and C4 below the lower limit of normal for testing laboratory. <sup>c</sup>Active nephritis or renal item on SLEDAI-2K (haematuria, proteinuria, pyuria or casts). 25(OH)D: 25-hydroxyvitamin D; BP: blood pressure; CVD: cardiovascular disease; HOMA-IR: HDL, high-density lipoprotein; homeostatic model assessment of insulin resistance; LDL: low-density lipoprotein; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC: Systemic Lupus International Collaborating Clinics; T, 25(OH)D tertiles.

were in the lowest tertile (T1: 10–36 nmol/l), 393 (33.8%) were in T2 (37–60 nmol/l) and 372 (32.0%) were in T3 (61–174 nmol/l) (Table 2). Patients in the lowest 25(OH)D tertile were younger compared with those in the higher tertiles [30 (23,40) (T1) vs 34 (25, 45) (T2) and 35 (25, 46) years old (T3);  $P < 0.001$ ]. Patients in the lowest 25(OH)D tertile were mostly non-Caucasian (65% vs 35% Caucasian,  $P < 0.001$ ). Patients located in the 'low latitude' had higher median (IQR) 25(OH)D compared with those living in the 'middle latitude' and 'high latitude' areas [56 (40, 75) vs 47 (29, 66) nmol/l and 47 (29, 64) nmol/l;  $P < 0.001$  for both comparisons] (Fig. 1). Patients with active SLE disease (SLEDAI of  $\geq 6$ ) had

lower median (IQR) 25(OH)D [45 (28–60) vs 50 (32–70) nmol/l in patients with SLEDAI  $< 6$ ;  $P < 0.001$ ].

Lower vitamin D in patients with MetS

There were sufficient data to define the MetS diagnosis in 860/1163 patients (73.9%). At enrolment, 286/860 (33%) fulfilled the MetS classification criteria. MetS was more common in men (31.8% men vs 23.7% women;  $P = 0.04$ ) and those with MetS were older [38.6 (15.2) vs 33.0 (12.0) years;  $P < 0.001$ ]. Patients diagnosed with MetS were more likely to be non-Caucasian (51% vs 49% Caucasian,  $P = 0.04$ ). Patients diagnosed MetS

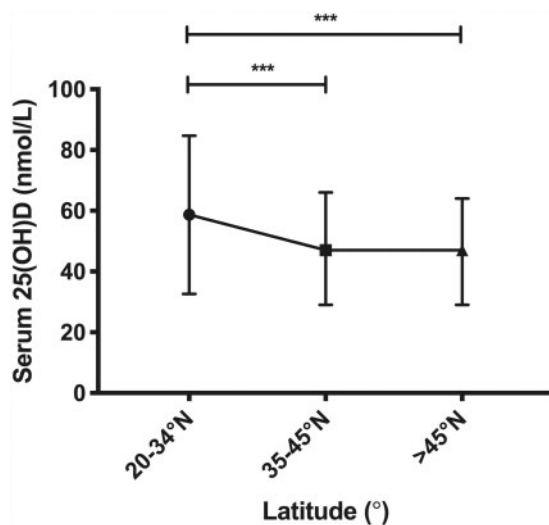
TABLE 2 Association between 25(OH)D tertiles and cardiovascular risk factors and SLE disease at baseline

CVD risk factors <i>n</i> (%) / median (IQR)	Vitamin D tertile (range)			<i>P</i> -value
	T1 ( <i>n</i> = 398) 10–36 nmol/l	T2 ( <i>n</i> = 393) 37–60 nmol/l	T3 ( <i>n</i> = 372) 61–174 nmol/l	
Age (years)	30.2 (23.0, 39.7)	34.3 (24.9, 44.7)	34.7 (25.1, 45.6)	<0.001
BMI, kg/m <sup>2</sup>	23.1 (20.2, 27.4)	24.5 (21.5, 28.4)	23.9 (21.6, 27.5)	0.22
Waist circumference, cm	79.0 (71.7, 90.0)	82.0 (74.0, 91.2)	80.0 (73.0, 89.0)	0.32
CVD risk factors				
Hypertension	161/391 (41.2)	149/382 (39.0)	110/363 (30.3)	0.005
Systolic BP (mm Hg)	120 (110, 130)	120 (110, 130)	120 (109, 126)	0.04
Diastolic BP (mm Hg)	74 (70, 80)	76 (70, 82)	72 (68, 80)	0.005
Anti-hypertensive medication	126/398 (31.7)	117/393 (29.8)	79/372 (21.2)	0.003
Total cholesterol (mmol/l)	4.7 (3.9, 6.0)	4.6 (3.9, 5.5)	4.4 (3.8, 5.1)	<0.001
Serum triglyceride (mmol/l)	1.6 (1.1, 2.2)	1.4 (1.0, 2.0)	1.2 (0.9, 1.6)	<0.001
HDL (mmol/l)	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)	1.4 (1.1, 1.7)	0.76
Lipid-lowering medication	60 (15.1)	28 (7.1)	24 (6.5)	<0.001
Fasting glucose (mmol/l)	4.8 (4.3, 5.4)	4.8 (4.3, 5.4)	4.7 (4.1, 5.2)	0.33
Fasting insulin (uIU/ml)	3.8 (2.0, 6.9)	3.4 (1.9, 5.1)	2.4 (1.8, 3.3)	<0.001
HOMA-IR	0.8 (0.4, 1.7)	0.7 (0.4, 1.1)	0.5 (0.4, 0.7)	<0.001
MetS Criteria				
MetS BP	183/392 (46.7)	192/383 (50.1)	140/364 (38.5)	0.005
MetS TG	182/354 (51.4)	135/326 (41.4)	84/319 (26.3)	<0.001
MetS HDL	156/240 (65.0)	114/220 (51.8)	89/209 (42.5)	<0.001
MetS Glu	71/346 (20.5)	70/326 (21.5)	55/321 (17.1)	0.35
MetS WC	158/356 (44.4)	172/332 (51.8)	131/299 (43.8)	0.07
Metabolic syndrome	115/303 (38.0)	103/280 (36.8)	68/277 (24.6)	<0.001
SLE-related characteristics				
SLEDAI-2K	4 (2, 8)	4 (2, 8)	4 (1, 6)	<0.001
Positive dsDNA	166/355 (46.8)	149/367 (40.6)	135/350 (38.6)	0.07
Low complement	171/360 (47.5)	148/373 (39.7)	121/351 (34.5)	0.002
CRP (mg/l)	3.9 (2.0, 7.0)	3.2 (2.0, 6.0)	2.9 (1.0, 6.6)	0.23
Creatinine (umol/l)	62 (59, 77)	70 (62, 80)	71 (62, 80)	0.09
Glucocorticoids				
Glucocorticoids	303 (76.1)	278 (70.7)	220 (59.1)	<0.001
Average GC dose (mg/day)	15 (4, 30)	13 (0, 27)	6 (0, 18)	<0.001
Anti-malarial therapy	264/397 (66.5)	274/393 (69.7)	290/371 (78.2)	0.001

Comparisons between 25(OH)D tertiles of continuous variables were carried out using one-way analysis of variance (ANOVA) and categorical variables by chi-squared test. CVD: cardiovascular; GC: glucocorticoids; HDL: high-density lipoprotein; HOMA-IR: homeostatic model of assessment of insulin resistance. Defined according to the metabolic S (MetS) criteria [15]: MetS BP, elevated blood pressure  $\geq 130/85$  or receiving anti-hypertensive medication; MetS HDL, reduced HDL  $< 1.3$  mmol/l in women and  $< 1.0$  mmol/l in men; MetS Glu: fasting glucose  $\geq 5.6$  mmol/l or being prescribed medication for hyperglycaemia; MetS TG: elevated serum triglyceride of  $\geq 1.7$  mmol/l or being on lipid-lowering medication; MetS WC: elevated waist circumference using gender and ethnicity-specific thresholds.



**Fig. 1** 25(OH)D levels [mean (IQR)] and sun exposure based on latitude ( $^{\circ}$ N) of patients ( $***P < 0.0001$ )



had a higher the median (IQR) HOMA-IR was than those who did not have MetS [0.9 (0.6, 1.8) vs 0.6 (0.3, 1.0),  $P < 0.001$ ]. Patients with MetS were more likely to have lower median (IQR) 25(OH)D than those without MetS [43 (28, 59) vs 49 (30, 70) nmol/l;  $P < 0.0001$ ].

#### Factors associated with lower vitamin D in SLE

In univariate linear regression models, lower 25(OH)D was associated with higher diastolic blood pressure, total cholesterol, serum triglyceride, fasting insulin and HOMA-IR, and low HDL levels (Table 3). Lower 25(OH)D was also associated with higher SLEDAI-2K scores, CRP, serum creatinine and glucocorticoid exposure. After adjusting for age, gender, latitude and ethnicity, lower 25(OH)D remained significantly associated with these outcomes, but not with serum creatinine and HDL.

In a logistic regression analysis, lower 25(OH)D was associated with MetS criteria of blood pressure, raised triglycerides and lower HDL (Table 4). After adjusting for age, latitude and ethnicity, these associations remained significant (variables contributing to individual MetS criteria such as gender in MetS HDL and gender and ethnicity in MetS WC were not included in the adjusted regression models). The association between lower 25(OH)D and MetS also remained in adjusted models.

We also found an association between lower 25(OH)D and an increased average daily oral glucocorticoid exposure, which remained significant after adjusting for disease activity and active renal disease [OR (95% CI): 0.93 (0.88, 0.98),  $P = 0.01$ ]. Average glucocorticoid exposure was also associated with increased insulin resistance (HOMA-IR) in the 396 patients who had fasting insulin and glucose samples.

We also repeated our logistic regression analyses on the subset who had no missing data to classify MetS

( $n = 548$ ). The associations between lower 25(OH)D and MetS remained significant (data on file). In addition, the association between lower 25(OH)D and MetS remained in adjusted models, which also included social factors such as current smoking status, known to be a risk factor in the context of MetS (data on file).

We then performed a ROC curve analysis to identify variables associated with the diagnosis of MetS in patients with SLE. Renal disease and average glucocorticoid exposure were risk factors associated with MetS in SLE, producing an area under the ROC curve (AUC) of 0.6488. Adding vitamin D levels to the model improved the AUC from 0.6488–0.6578 ( $P = 0.20$ ) (Fig. 2).

## Discussion

In a large international cohort of SLE patients, we have found an association between lower 25(OH)D and MetS as well as elevated markers of insulin resistance. In our regression analyses, lower vitamin D remained associated with MetS after adjustment for other SLE related factors.

The reasons for a higher prevalence of MetS in patients in the lowest 25(OH)D tertile are not well understood. Patients with lower 25(OH)D were more likely to have increased disease activity, in agreement with some previous [25–27], but not all, cross-sectional studies [28, 29] and in part may reflect vitamin D being a negative acute phase reactant [30]. Given that photosensitivity is a key feature of SLE, it is also likely that sun avoidance, the usage of high-factor sunblock and living further from the equator contributes to lower 25(OH)D levels. We therefore estimated sun exposure using the latitude of recruiting centre location, as the amount of ultraviolet in ambient sunlight varies greatly by latitude [24]. The centre locations ranged between 20 $^{\circ}$ N and over 45 $^{\circ}$ N and significantly higher 25(OH)D was observed in patients living closer to the equator despite the hypothesis that sun-seeking behaviour is less common in this part of the world due to the hotter climate [31].

Patients with lower 25(OH)D were more likely to have MetS and this association was significant after adjusting for age, latitude and BMI. Our results suggest that co-existing physiological abnormalities may contribute to long-term cardiovascular risk early on in SLE. In animal models of SLE, 25(OH)D deficiency is associated with endothelial dysfunction and impaired angiogenesis [11]. Similarly, in SLE patients treated for vitamin D deficiency, improvement in endothelial function correlated with the increment of 25(OH)D and may be related to changes in myeloid angiogenic cell function [32]. In agreement with trends seen in the general population and patients with SLE, we found significant associations between lower 25(OH)D and recognized cardiovascular risk factors including hypertension and low HDL [12, 14, 33, 34]. We also found a significant association between lower 25(OH)D and hypertriglyceridemia in adjusted models. The mechanisms underlying these associations

**TABLE 3** Association between 25(OH)D and cardiovascular risk and SLE factors at baseline

CV risk factors	Unadjusted			Adjusted model 1 <sup>c</sup>			Adjusted model 2 <sup>d</sup>		
	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value
Waist	-0.01	-0.35, 0.33	0.96	-0.18	-0.51, 0.16	0.30	-0.17	-0.36, 0.03	0.10
Systolic BP	-0.29	-0.67, 0.10	0.14	-0.56	-0.93, -0.20	0.003	-0.57	-0.93, -0.21	0.002
Diastolic BP	-0.26	-0.51, -0.02	0.04	-0.32	-0.57, -0.07	0.01	-0.32	-0.57, -0.07	0.01
Total cholesterol	-0.10	-0.13, 0.06	<0.001	-0.10	-0.14, -0.07	<0.001	-0.10	-0.14, -0.07	<0.001
Triglyceride <sup>a</sup>	-0.05	-0.06, -0.04	<0.001	-0.05	-0.07, -0.04	<0.001	-0.05	-0.07, -0.04	<0.001
HDL cholesterol <sup>a</sup>	0.01	0.002, 0.03	0.02	0.01	-0.001, 0.02	0.08	0.01	-0.001, 0.03	0.08
Fasting glucose	-0.02	-0.06, 0.03	0.47	-0.04	-0.08, 0.01	0.08	-0.04	-0.09, 0.01	0.09
Fasting insulin <sup>a</sup>	-0.06	-0.10, -0.03	<0.001	-0.05	-0.09, -0.02	0.002	-0.05	-0.09, -0.02	0.002
HOMA-IR <sup>a</sup>	-0.07	-0.12, -0.03	<0.001	-0.06	-0.10, -0.02	0.003	-0.06	-0.10, -0.02	0.002

SLE factors	Unadjusted			Adjusted model 1 <sup>c</sup>			Adjusted model 2 <sup>d</sup>		
	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value
SLEDAI-2K <sup>b</sup>	-0.11	-0.15, -0.07	<0.001	-0.10	-0.15, -0.06	<0.001	-0.11	-0.15, -0.06	<0.001
CRP <sup>a</sup>	-0.05	-0.09, -0.02	0.002	-0.06	-0.10, -0.03	0.001	-0.07	-0.10, -0.03	<0.001
Creatinine <sup>a</sup>	0.01	0.001, 0.02	0.03	0.003	-0.004, 0.01	0.36	0.003	-0.004, 0.01	0.34
Average GC <sup>a</sup>	-0.06	-0.08, -0.04	<0.001	-0.06	-0.08, -0.04	<0.001	-0.06	-0.08, -0.03	<0.001

<sup>a</sup>Log transformed variables. <sup>b</sup>Ordered logistic regression (SLEDAI-2K expressed in tertiles). <sup>c</sup>Adjusted model 1: controlled for age, gender, average latitude and ethnicity. <sup>d</sup>Adjusted model 2: as in adjusted model 1<sup>c</sup>, and including BMI.  $\beta$ :  $\beta$ -coefficient; BP: blood pressure; CV: cardiovascular; GC: glucocorticoid; HOMA-IR: homeostatic model of assessment of insulin resistance.



TABLE 4 Association between 25(OH)D and individual binary cardiovascular risk criteria contributing to MetS

CV risk factors required for a MetS diagnosis	Unadjusted			Adjusted model 1 ( <sup>c</sup> unless specified)			Adjusted model 2 ( <sup>d</sup> unless specified)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Hypertension	0.94	0.90, 0.99	0.02	0.92	0.88, 0.97	0.003	0.92	0.87, 0.97	0.003
Hypertriglyceridemia	0.85	0.80, 0.89	<0.001	0.84	0.79, 0.89	<0.001	0.83	0.79, 0.89	<0.001
HDL (low/high) <sup>a</sup>	0.86	0.81, 0.92	<0.001	0.88	0.82, 0.94	<0.001	0.88	0.82, 0.94	<0.001
Hyperglycaemia	0.95	0.89, 1.02	0.147	0.92	0.86, 0.99	0.02	0.92	0.85, 0.99	0.02
Waist circumference (low/high) <sup>b</sup>	1.00	0.95, 1.05	0.969	0.97	0.92, 1.02	0.289	0.94	0.88, 1.01	0.08
Metabolic syndrome <sup>b</sup>	0.90	0.85, 0.96	0.001	0.86	0.81, 0.91	<0.001	0.85	0.79, 0.91	<0.001

CV: cardiovascular; OR: odds ratio. <sup>c</sup>Adjusted model 1: controlled for age, gender, average latitude and ethnicity. <sup>d</sup>Adjusted model 2: as in adjusted model 1<sup>c</sup>, and including BMI and current smoking status. <sup>a</sup>Adjusted model 1 and 2 without gender. <sup>b</sup>Adjusted model 1 and 2 without gender and ethnicity.

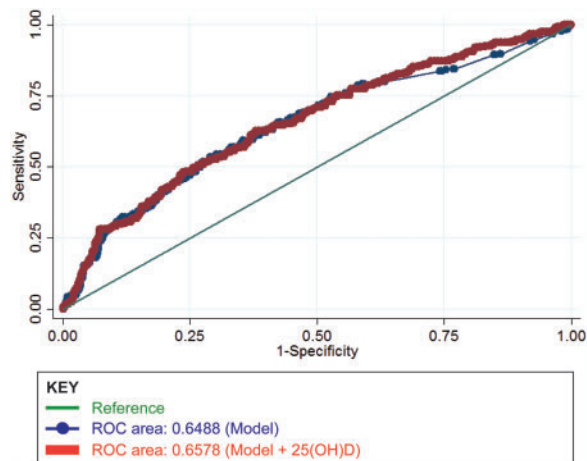
are not clear but may be linked to the negative feedback of 25(OH)D on the renin-angiotensin system [35, 36]. In the 322/1163 patients prescribed anti-hypertensive medication, there was a loss of association between lower 25(OH)D and the presence of some but not all cardiovascular risk factors (data not shown), which may justify the concurrent treatment of 25(OH)D levels; however, further studies are required to validate this strategy.

Insulin resistance, measured by elevated fasting serum insulin and HOMA-IR, is prevalent in the SLE population and has been linked to an increased risk of CVD [37, 38]. Previous studies have demonstrated in non-diabetic patients with SLE that elevated fasting insulin and HOMA-IR were both associated with lower 25(OH)D [13, 27]. We confirmed this finding and showed that lower 25(OH)D was associated with hyperglycaemia, which persisted in adjusted models. These findings are not surprising given the multifactorial contribution to increased cardiovascular risk and insulin resistance, which may be an early link to the heightened risk of developing MetS [39]. Our fasting insulin subset was smaller ( $n=396$ ). This is because not all centres were able to perform fasting blood samples due to clinic scheduling. Nevertheless, our study represents the largest and most diverse cohort thus far assessing the association between 25(OH)D and markers of insulin resistance.

Insulin resistance is known to be associated with obesity and glucocorticoid use in SLE [13] and, indeed, this was the case in our cohort. Hence, we adjusted for central obesity (MetS WC) and glucocorticoid exposure and found that the association between lower 25(OH)D and elevated fasting glucose and insulin persisted (data not shown). There was also an association between lower 25(OH)D and central obesity, which was significant only after adjusting for ethnicity and region. This may be in part due to a subset of patients of Korean ethnicity ( $n=156$ ) when compared with all other ethnicities, had a lower prevalence of central obesity (20.5% vs 51.4%;  $P=0.006$ ) and median (IQR) BMI [20.9 (18.9, 22.9) vs 24.5 (21.6, 28.5);  $P<0.001$ ], consistent with a previous analysis of the SLICC cohort [40]. Interestingly, patients of Korean descent compared with all other ethnicities had lower median (IQR) 25(OH)D [28 (20, 39) vs 51 (34, 69) nmol/l;  $P<0.001$ ]. We also found that a significantly higher proportion of patients in the Korean subset had raised triglycerides, low HDL and hyperglycaemia (data not shown). This suggested that an ethnic gradient may contribute to enhanced sensitivity to adverse effects of inflammation and an increased susceptibility to MetS [40].

There is evidence that glucocorticoids increase vitamin D catabolism by activating nuclear receptors, which triggers 25(OH)D breakdown through the expression of CYP3A4. Thus, it may be beneficial in such patients to increase vitamin D supplementation or minimise glucocorticoid exposure [41, 42]. Our study found an association between lower 25(OH)D and increased

**Fig. 2** Receiving operating characteristics (ROC) curve analysis for identifying variables predicting the diagnosis of MetS in patients with SLE



Renal disease and average glucocorticoid exposure were risk factors associated with MetS in SLE producing an area under the ROC curve (AUC) of 0.6488 (Model). Adding vitamin D to the model improved the AUC to 0.6578 [Model + 25(OH)D].

glucocorticoid exposure, which differed from previous work reporting no correlation between these variables [43, 44]. We also found that lower 25(OH)D was less likely in patients prescribed anti-malarial therapy, which has been seen in some [12, 28] but not all previous studies [43, 45]. Previous work has linked the potential and protective effect of anti-malarial medication against MetS in patients with mild to active SLE [18, 40, 46]. However, the relationship between anti-malarials and 25(OH)D levels in SLE is complex. As our study only included patients with a short exposure to medication in the context of active disease, the influence of longer-term exposure remains to be explored.

This is the largest study to date examining the associations between 25(OH)D levels and MetS in SLE; it also has the advantage of being an international cohort. The SLICC Inception Cohort recruited from 33 centres in 11 countries with diverse racial and ethnic backgrounds; therefore, results will be generalizable across many settings. Our cohort included younger patients with a wide range of disease activity, enabling effective investigation into the association of 25(OH)D with MetS and extends our previous findings to MetS and markers of insulin resistance. We also used a definition of MetS that recognizes that patients without central obesity can also be included in this phenotype [15]. Our population also contained detailed data on glucocorticoid exposure, which enabled detailed analysis of their associations with vitamin D levels.

Our study has several limitations worth considering. Of the total number of patients in the cohort, sample availability meant that 25(OH)D was not measured in 37.1%. It was not possible to measure 25(OH)D levels

from all patients due to blood samples not being available from some centres, for instance from patients in Mexico. The subset of patients without 25(OH)D data had similar demographics and disease activity to those who have had their levels measured, although the average glucocorticoid exposure was higher. However, our analyses within the cohort adjusted for these factors and so our associations are likely to remain valid. While 34.1% of patients reported taking vitamin D supplements, the dose taken was not available and therefore we were not able to accurately assess its effects in this cohort. Data were not available to confirm a MetS diagnosis in 26.1% of our patients with available 25(OH)D. Of the components required to fulfil a MetS diagnosis, HDL was the most commonly missing variable, as this test was not routinely performed in all centres. As stated in the results, using a complete case subset did not materially affect the results of our analysis. Also, while social determinants of health such as a more active lifestyle, a healthier diet etc may serve as confounders, such data was not available in our cohort, although adjusting for smoking status did not influence the associations observed. The use of MetS to predict CVD has not yet been validated in SLE; however, we do know that MetS susceptibility can be determined early in the SLE disease course and inform risk stratification in individual patients [20]. Finally, although the cross-sectional nature of this study prevents the determination of causal associations between MetS, markers of insulin resistance and lower 25(OH)D, our study provides important information required for prospective studies.

In patients with recently diagnosed SLE we report an association between lower vitamin D levels and both MetS and insulin resistance. This association may have a physiological basis linked to endothelial or vascular dysfunction. Increased susceptibility to MetS and cardiovascular risk factors in patients with low 25(OH)D may provide a mechanism to modify systemic inflammation in SLE. The significant association between increased glucocorticoid exposure and lower 25(OH)D also emphasizes the importance of minimizing glucocorticoid exposure in SLE. The potential role of vitamin D supplementation to improve cardiometabolic outcomes in SLE will require further trials and seems justified on the basis of our findings.

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## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary data

[Supplementary data](#) are available at *Rheumatology* online.

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