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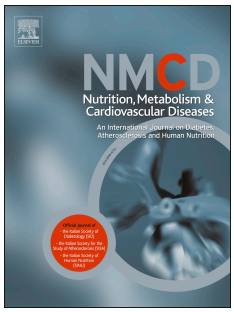

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Clinical and subclinical cardiovascular disease in female SLE patients: interplay between body mass index and bone mineral density

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ABSTRACT

Background and aims: since accelerated atherosclerosis has been reported in systemic lupus erythematosus (SLE), predictive biomarkers of cardiovascular disease (CVD) are needed. Among non-traditional risk factors, bone mineral density (BMD) has been related to CVD. However, its role in SLE remains controversial. This study aims to analyze the associations of subclinical atherosclerosis with traditional and non-traditional CV risk factors.

Methods and results: in a cross-sectional study, atherosclerosis burden was compared between 112 female SLE patients and 31 controls. Plaque number and carotid intima-media wall thickness (cIMT) were assessed by ultrasonography. In a retrospective study, BMD determinations obtained 5-years before the ultrasonography assessment were analyzed in a subgroup of 62 patients. Plaque frequency was increased in SLE, even in patients without CV events or carotid wall thickening. cIMT was increased in patients with CVD, positively correlated with body mass index (BMI). Interestingly, a paradoxical effect of BMI on carotid parameters was observed. Whereas underweight patients (BMI<20) showed increased prevalence of carotid plaques with low cIMT, those with BMI>30 showed higher cIMT and plaque burden. Overweight patients (25<BMI<30) exhibited both elevated cIMT and plaque number. BMI was an independent predictor of BMD. In our retrospective study, patients with either clinical or subclinical CVD exhibited lower BMD levels than their CV-free counterparts. A low lumbar spine BMD independently predicted CVD development after adjusting for confounders.

Conclusion: SLE was associated with a higher subclinical atherosclerosis burden, a bimodal effect being observed for BMI. Decreased BMD can be a CV risk biomarker in SLE.

Keywords: systemic lupus erythematosus, atherosclerosis, bone mineral disease, body mass index, subclinical cardiovascular disease

INTRODUCTION

Cardiovascular disease (CVD) has a major impact on morbidity and mortality in systemic lupus erythematosus (SLE) (1), the prototypical systemic autoimmune disease. Recent evidence suggests an increased CV risk in patients at early disease stages or even at diagnosis. An increased prevalence of subclinical atherosclerosis, assessed by presence of carotid plaque and/or arterial wall thickening, has been observed in SLE patients (2–4). Moreover, subclinical atherosclerosis has been reported in young SLE patients without traditional risk factors (5). Actually, traditional CV risk cannot fully account for the increased CVD occurrence in SLE (6–8), hence supporting a role for chronic inflammation, autoimmunity and other SLE-related features. Therefore, the identification of novel biomarkers to be used in the clinical setting to identify patients at risk represents a major unmet need in this scenario.

In recent years, a possible relationship between reduced bone mineral density (BMD) and CVD has emerged. BMD is also affected by inflammation and immune over-activation, and altered BMD is a frequent hallmark of SLE patients. The relationship between BMD and vascular calcifications was firstly described some time ago (9), but this association was probably under-estimated, since osteoporosis and vascular calcifications were originally considered as non-modifiable disorders of ageing. Currently, although the role of ageing cannot be completely dismissed, age-independent, direct biological links between bone metabolism and CVD have been described(10,11). However, the associations between bone metabolism and surrogate markers of CVD other than vascular calcification are under debate. In fact, contradictory results about the association between BMD and carotid atherosclerosis have been reported in SLE (12,13). Interestingly, reduced BMD has been associated with endothelial dysfunction in SLE (14), pointing to a very early crosstalk between BMD and CVD.

Taking all these ideas into account, we aimed to evaluate (i) the prevalence of subclinical CVD (measured as atherosclerotic plaques and carotid arterial wall thickening) in SLE patients and the potential associations with traditional and non-traditional CV risk factors and (ii) the predictive value of 5-years retrospective BMD determination for the development of CVD in SLE.

MATERIAL AND METHODS

Patients and controls

This study encompasses both a cross-sectional and a retrospective sub-analyses. Our cross-sectional study involved 112 female SLE outpatient patients and 31 matched healthy volunteers from the same population as controls (see Online Supplementary Material). All patients fulfilled the American College of Rheumatology (ACR) revised criteria for the SLE classification (15). Traditional CV risk factors, parameters of disease activity (anti-dsDNA titer and SLE disease activity index, SLEDAI) and treatments received was obtained from clinical records (See Online Supplementary Material). A CV event was defined as previously described (16). For the retrospective sub-analysis, a subgroup of 62 female SLE patients who underwent a bone mass densitometry determination 5-years before the recruitment for the study was selected. Clinical features and demographic parameters at the time of BMD assessment were included in the analyses.

Ethics approval was obtained from the Institutional Review Board (Regional Ethics Committee for Clinical Research, Servicio de Salud del Principado de Asturias, reference PI-16/00113), according to the Declaration of Helsinki. Written informed consent was signed from all individuals prior to enrollment.

Carotid ultrasound assessments

Doppler ultrasound assessment was performed using a Toshiba Aplio XG machine. The carotid intima-media wall thickness (cIMT) was bilaterally measured according to the "Mannheim Carotid Intima-Media Thickness Consensus (2004-2006)" (17) (see Online Supplementary Material). Plaque prevalence was considered as the frequency of patients exhibiting at least one plaque according to the previous consensus definition.

Bone mineral density measurements

Bone mineral density (BMD) was measured using a Hologic® QDR-4500 DXA densitometer. Both the postero-anterior lumbar spine (L2-L4) and the right proximal femur were analysed. Osteoporosis was defined according to World Health Organisation (WHO) criteria (18,19) (see Online Supplementary Material). Z- and T-scores were also calculated with the reference lumbar spine and proximal femur bone values of the Spanish population (19).

Vascular calcifications were evaluated by X-rays (see Online Supplementary Material) (9,20,21), and the presence of osteoarthritis lesions was determined according to the Kellgren-Lawrence scale.

Statistical analyses

Variables were summarized as mean ± standard deviation, median (interquartile range) or n(%), as appropriate. Differences between continuous variables were analysed by T, Mann-Withney U or Kruskal Wallis tests. For categorical variables, χ^2 tests were performed. Multivariate analyses were carried out by multiple linear regression models or binary logistic regression. Demographic parameters, clinical features and traditional CV risk factors were entered in the models as covariates, as indicated. Odds Ratios (OR) and Relative Risk (RR), for binary logistic regression and B for linear regression, together with their respective 95% confidence intervals (CI) were computed (see Online Supplementary Material). A p-value<0.050 was considered the limit of statistical significance.

RESULTS

Increased prevalence of subclinical atherosclerosis in SLE

The presence of carotid atherosclerotic plaques and wall thickness (cIMT) in both left and right arteries were evaluated as surrogate markers of subclinical atherosclerosis in 112 female SLE patients and 31 matched healthy controls (HC). Demographic parameters, traditional CV risk factors and clinical features of the subjects involved in the study are summarized in the Supplementary Table 1. SLE patients showed increased prevalence of hypertension and obesity (BMI>30) and 16 of them have a previous history of CV events. Vascular ultrasonography revealed higher frequency of carotid plaques in SLE patients compared to HC (30.3% vs 9.6%, p=0.020), mainly in the left branch (Table 1). These findings were more evident in those who had suffered a CV event (Table 1). The mean number of plaques was also higher in patients, even in those without CVD (p=0.045). Conversely, the cIMT was only significantly increased in patients with previous CVD, thus supporting that SLE patients may present atherosclerotic plaques even in the absence of increased cIMT.

Multivariate regression analysis including sex, age and traditional CV risk factors (dyslipidemia, hypertension, obesity and smoking habit) revealed that SLE patients presented more than 2-fold risk than HC for the development of atherosclerotic plaques (Table 2). A similar result was obtained when patients with previous CVD were excluded from the analysis (RR[95% CI]: 2.63[1.03, 8.50], p=0.038). Additionally, controlling for glucocorticoid usage at recruitment and ever use of high doses since diagnosis did not modify the association between SLE and plaque burden (RR[95% CI]: 2.50[1.06, 7.89], p=0.039). Interestingly, a multivariate analysis in SLE patients including traditional CV risk factors, disease activity and duration, previous CVD and treatments (including current and ever use high doses of glucocorticoids) in the model (Supplementary Table 2) showed an unexpected protective role for BMI in the development of carotid plaques (RR[95% CI]: 0.92[0.87, 0.98], p=0.015). Conversely, BMI was positively correlated with cIMT in patients (r=0.335, p<0.001), even after adjusting for sex, age and disease activity, duration and therapy usage (including current use of glucocorticoids and ever use of high doses of glucocorticoids, antimalarials and immunosuppresants) (β=0.253, p<0.001). Interestingly, patients with BMI>25 (n=55) exhibited an increased cIMT compared with the under- and normal weight patients (p<0.001) and the HC group (p=0.022). Concurrent analysis of carotid plaques and cIMT in SLE patients categorized according to BMI showed that both under- and overweight patients exhibited higher prevalence of carotid plaques, hence suggesting a bimodal pattern, whereas cIMT was exhibited an increase in the overweight group and plateauing beyond BMI>30 (Figure 1).

Interestingly, quadratic curve fitting showed no increase in cIMT above BMI>30 (Figure 1). Exclusion of SLE patients with CVD from the analysis retrieved similar findings. Glucocorticoid usage was similar among BMI groups (p=0.432).

Finally, we evaluated whether any SLE-related factors could be associated with the presence of carotid plaques using a multivariate logistic regression model. In a backward multistep analysis entering demographic variables, clinical features, treatments (including current use of glucocorticoids and ever use of high doses of glucocorticoids) and traditional CV risk factors in the initial model, only age (RR[95% CI]: 1.13[1.06, 1.20], p<0.001) and (RR[95% CI]: 2.51[1.02, 7.42], p=0.043) showed a significant association.

These results confirm an increased prevalence of subclinical atherosclerosis in female SLE patients and a paradoxical bimodal effect of BMI. Important differences between cIMT and plaque occurrence were disclosed.

Low lumbar spine mineral density as a prognostic factor for CVD

The possible predictive value of low bone mineral density (BMD) for the development of CVD was analyzed in a subgroup of 62 female SLE patients in whom the BMD at lumbar spine, femoral neck, total hip and Ward triangle had been determined 5 years before the vascular ultrasound examination. This subgroup was representative of the whole cohort of SLE patients regarding demographic, clinical and traditional CV risk factors. Data of BMD (g/cm^2), T-score and Z-score at all bone sites, and concurrent clinical data (Supplementary Table 3), were analyzed in relation to the current CVD status, either clinical CVD or subclinical CVD (considered as presence of carotid plaques) (Figure 2).

Interestingly, patients with either clinical or subclinical CVD exhibited a lower value of BMD 5 years before, especially at lumbar spine. Therefore, both CVD groups were grouped and analyzed together thereafter. A logistic regression model including all bone mineral measurements, age, BMI, usage of high doses of glucocorticoids (>7.5 mg/day ever since diagnosis), immunosuppressants (since diagnosis), history of previous fractures, menopause status, and the presence of osteoarthritis lesions and vascular calcifications at the time of densitometry, revealed that low lumbar spine mineral density was an independent predictive factor for CVD development (Table 3). Actually, low lumbar BMD (defined either as osteopenia [n=18] or osteoporosis [n=12] according to the reference values) was associated with an increased risk of CVD development (OR[95% CI], p: 6.411[1.134, 36.239], p=0.036) after adjusting for potential confounders. Importantly, this

association was already observed in patients with osteopenia (5.161[1.126, 52.181], p=0.040), whereas a separate analysis on their osteoporosis counterparts alone did not exhibit such association (1.276[0.090, 18.080], p=0.857). Interestingly, BMD determinations at any bone site were not predictive of cIMT values (Supplementary Table 4).

It is noteworthy that BMI (at the time of densitometry) was an independent predictor of BMD at all bone sites in linear regression analyses adjusted for age (lumbar spine: β=0.317, p=0.028; femoral neck: β=0.516, p<0.001; total hip: β=0.473, p=0.001, and Ward triangle: β=0.289, p=0.072). Use of high dosages of glucocorticoids (either at the time of BMD measurement and ever use since diagnosis) was not found to have an effect on these associations. Similarly, these associations remained after controlling for menopause and history of previous fractures. Moreover, no association was found between BMD and presence of vascular calcifications or osteoarthritis lesions.

Overall, our findings confirm that a low BMD can be an independent predictor of CVD occurrence in SLE patients. Additionally, a positive association between BMI and BMD is disclosed.

DISCUSSION

Although a compelling body of evidence supports an increased prevalence of CVD in SLE, the origin of this increased risk remains elusive and new biomarkers allowing early identification of patients at risk are needed. Apart from vascular homeostasis, bone metabolism has been largely reported to be altered in SLE. In the present work we have explored the potential links between these two conditions and we have reported, for the first time, that a low BMD at lumbar spine predict clinical and subclinical CV events occurrence in female SLE patients. Additionally, a paradoxical bimodal effect of BMI on atherosclerosis burden was observed.

In line with the prevalence reported by other authors (2–4), about one third of our SLE patients presented carotid plaques, suggestive of subclinical atherosclerosis, even in the absence of a substantial cIMT increase. In fact, a significant arterial wall thickening was only detected in patients with CVD, whereas SLE patients without previous history of CV events have near 3-fold higher frequency of carotid plaques than controls after adjusting for traditional CV risk factors. These results highlight important differences between both ultrasound findings. Although frequently considered as synonymous assessments, our results underline important differences between them, in line with other studies in immune-mediated conditions (22,23). Of note, cIMT not only represents subclinical atherosclerosis but it is also influenced by non-atherosclerotic wall remodeling (17). However, the presence of plaque is of overriding importance in reflecting cardiovascular risk (24). Therefore, all these lines of evidence point to a complementary, different interpretation of cIMT and plaque number, especially in immune-mediated diseases. Whether these discrepancies are also the consequence of different underlying mechanisms warrants further studies.

An interesting result from our study was the apparently paradoxical effect of the BMI on the development of subclinical atherosclerosis in SLE. The worst carotid parameters, high both cIMT and plaque number, were observed in overweight patients. However, underweight (BMI<20) was found to be detrimental for plaque development with no effect on cIMT, whereas obese patients (BMI>30) were less likely to exhibit carotid plaques in spite of the increased cIMT. All these findings reflect the complex relationship between BMI and CVD and are in agreement with the so-called “obesity paradox”, a term coined to explain the epidemiologic observation of a protective effect of obesity on CVD outcomes in several studies (25–27). A number of quantitative and qualitative concepts emerge from these findings. First, from a quantitative point of view, although high BMI has been largely recognized as an independent CV risk factor in the general population, recent epidemiological studies have challenged this notion by reporting better survival outcomes in obese patients than in their non-obese counterparts in a wide range of chronic diseases, from heart

failure and other CVD to chronic kidney disease (28), chronic obstructive lung disease (29), hypertension, type 2 diabetes (30), rheumatoid arthritis (31) or osteoporosis (32). Interestingly, Sacre and colleagues have found that overweight is the main contribution to atherosclerosis in SLE patients (33). However, no separate analysis of underweight and obese patients has been performed, which makes difficult the comparison between studies. On the other hand, a non-linear effect of BMI has been reported elsewhere (34,35), which is in accordance with our results. These findings may suggest that the effect of obesity cannot be solely explained by the quantity of adipose tissue, hence pointing to qualitative aspects such us its composition, metabolic status or location in the body. As a consequence, a multifactorial origin emerges from the obesity paradox, thus explaining, at least partially, the heterogeneous results obtained elsewhere.

In fact, there are some pieces of evidence underlining the limitations of the use of BMI as a measure of obesity (36). This is especially evident in immune-driven conditions, where an altered body composition is widely recognized (37,38) and anthropometrical measures have yielded contradictory results (39). It is important to note that body composition, and thus the qualitative effects of obesity, may also differ by gender. However, our study was focused on female SLE patients, hence allowing us to avoid a potential confounding effect of gender. Additionally, other mechanisms associated to adipose tissue are probably involved, such as the secretion of a variety of adipokines or soluble receptors, with different, and frequently controversial, effects on CVD (40–44). Finally, several studies have revealed some controversy with regards to the association between BMI and cIMT or plaque numbers (12,13), different associations being observed for each surrogate marker. On the one hand, these findings add to the current complexity of the “obesity paradox”. On the other hand, these divergent associations may point to different mechanisms underlying cIMT and plaque development in SLE, thereby supporting our previous results. Interestingly, Ajeganova and colleagues found a considerable number of clinical parameters independently associated with plaque formation in SLE patients, including low C4, disease duration and activity score, but not for cIMT, which was strongly associated with BMI (13). Our analyses revealed an association of plaque burden with the presence of serositis, a complication of SLE. Taken together, these data lead us to consider that plaque development may be more actively influenced by chronic inflammation and impaired immune response, whereas the cIMT may be more dependent of the BMI, probably because of hemodynamic factors (36).

Overall, the results herein reported allow us to propose a new CV-protective mechanism of adipose tissue, at least in female SLE patients, since a decreased BMD, associated to a low BMI, was a clear predictive factor of CVD in these patients. The predictive value of a low BMD for the development

of CVD in SLE patients detected in this study is in line with the relationship between osteoporosis and atherosclerosis reported in several large observational studies (45–47). However, contradictory results have been found in SLE patients, since both an association between BMD and carotid plaques (13) and a lack of it (12) have been recently reported. Nevertheless, methodological differences between studies must be acknowledged. Since both atherosclerosis development and bone turnover are progressive, long-lasting processes, we evaluated the predictive potential of BMD assessment for the development of clinical or subclinical CVD along the disease course. We found that low BMD at lumbar spine can be proposed as a novel CV risk factor in female SLE patients. Importantly, although previously linked to endothelial dysfunction (14), our findings were further by demonstrating an association with both clinical and subclinical CVD occurrence in SLE. Interestingly, glucocorticoids usage was not associated with CV endpoints in our study, hence ruling out the possibility of a potential confounding effect (either by indication bias or a potential glucocorticoid-dependent bone loss). Moreover, our results showed a predictive value of low BMD even at subclinical osteopenia levels, hence expanding the established idea about the association between clinical osteoporosis and CVD and adding ~~to~~ the clinical value to the subclinical bone loss in this setting.

It could be hypothesized a protective effect of adipose tissue in SLE patients that could be partly attributed to the preservation of an adequate mineral density over time, whereas at low BMI the bone loss is enhanced. Actually, our results confirm a positive association between BMI and BMD. Low BMI is a well-known risk factor for decreased BMD and fragility fracture (32,48). Nevertheless, a larger BMI confers greater mechanical loading on bone, enhancing its capacity to accommodate the heavier load. Hence, it is feasible that a low BMI may be related to an altered bone storage capacity, which may ultimately affect the promotion of atherosclerosis, hence suggesting a link among BMI, bone metabolism and (cardio)vascular homeostasis along disease course.

Finally, although different bone locations were analyzed in the present study, only lumbar spine remained as an independent predictor of CVD development in multivariate analyses. Similar results were published by our group (20) when looking at vascular calcifications. These results reinforce the idea that bone loss might occur first in trabecular bone (lumbar spine) instead in cortical bone (proximal femur), as previously suggested (49). This is also in line with previous studies by other groups in SLE (50). Consequently, this will facilitate the implementation of BMD as a novel risk biomarker in the clinical setting. The strong association between low BMD and CVD occurrence proved these findings worthy of further research to improve clinical management in this condition.

Similarly, although our results confirm its predictive value over a 5-years period, whether other time-points may be useful requires further elucidation.

In summary, our findings confirm an increased prevalence of subclinical atherosclerosis in female SLE patients compared to healthy controls. Whereas plaque development was observed in patients free of CV events, cIMT was only increased in those with a history of previous CVD and in patients with high BMI. Furthermore, although age and serositis were independently associated with atherosclerotic plaques, a paradoxical association was observed for BMI. Additionally, the most striking finding, not previously reported, was that sub-clinically low BMD, beyond the osteoporosis threshold, at lumbar spine emerged as an independent CVD predictor in a retrospective analysis. Importantly, low BMD was associated with a low BMI, thus suggesting a crosstalk between bone metabolism and cardiovascular traits in SLE. It is important to consider that our study was developed under a retrospective design and, as such, intrinsic bias may represent a potential limitation. However, an appropriate management and analysis of clinical datasets to minimize its possible effect was performed.

HIGHLIGHTS

- Atherosclerosis is found in female SLE patients without CV disease (CVD) or increased cIMT
- A paradoxical, negative association between obesity and plaque burden is found
- BMI is an independent predictor of bone mineral density (BMD) in female SLE patients
- Low BMD predicts clinical or subclinical CVD development in SLE

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FIGURE LEGENDS

Figure 1: Association between BMI and cIMT in SLE female patients. Our data showed fitted best to a quadratic curve fitting. No effect of BMI beyond 30 kg/m^2 was observed on cIMT values. However, a bimodal distribution was observed for plaque development. Patients with obesity exhibited the lowest plaque number among BMI groups (table below graph). Presence of carotid plaques was calculated as the frequency of patients with at least one plaque within the group sample population (indicated in each column. Differences were assessed by Kruskal-Wallis or χ^2 test.

Figure 2: Analysis of retrospective BMD determinations and CV status in female SLE patients. BMD determinations (BMD, T-score and Z-score) at different bone sites (lumbar spine, femoral neck, total hip and Ward triangle) obtained 5 years before ultrasonography determination were compared in SLE patients among groups: no CVD (free of CV events, n= 33), subclinical CVD (defined as the presence of carotid plaques, n=16) and CVD (occurrence of a past CV event, n=13). BMD values are represented according to left Y-axis (g/cm^2), whereas those of Z- and T-scores are to the left Y-axis (score). Boxes represent median as well as first and third quartiles, and the lines outside the boxes represent the minimum and maximum values. Differences were evaluated by Kruskal-Wallis test and Dunn-Bonferroni correction for multiple comparisons tests.

Table 1. Prevalence of atherosclerotic plaques in controls and SLE patients.

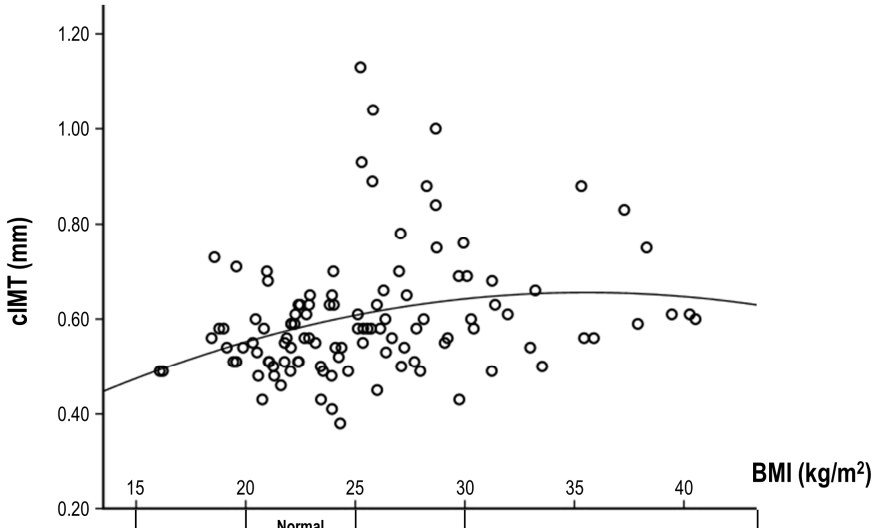
	HC (n=31)	SLE without CVD (n=96)	SLE with CVD (n=16)	p-value
Presence of carotid plaques[a], n (%)				
Left	2 (6.5)	21 (21.9)	6 (37.5)	0.034
Right	3 (9.7)	21 (21.9)	5 (31.3)	0.174
Left + Right	3 (9.7)	26 (27.1)	8 (50.0)	0.009
Plaque number, mean ± SD	0.13 ± 0.42	0.49 ± 0.87	0.81 ± 0.50	0.014
cIMT (mm), median (IQR)				
Left	0.56 (0.07)	0.56 (0.10)	0.70 (0.24)	0.022
Right	0.56 (0.16)	0.56 (0.19)	0.58 (0.19)	0.240
Mean	0.56 (0.12)	0.57 (0.10)	0.67 (0.21)	0.044

Variables were summarized as mean±SD, median (IQR) or n(%). [a] Presence of carotid plaques was calculated as the frequency of patients with at least one plaque within the whole population. Statistical differences were assessed by Kruskal-Wallis or χ^2 tests, as appropriate. cIMT: coronary intima-media thickness.

Table 2. Relative risk for change in the number of atherosclerotic plaques in SLE compared with controls.

	Relative risk	95% CI	p-value
SLE	2.884	1.027, 8.098	0.039
Age	1.074	1.038, 1.111	<0.001
BMI	0.710	0.563, 0.980	0.040
Smoking	1.446	0.636, 3.289	0.378
Dyslipidemia	1.167	0.482, 2.823	0.732
Hypertension	1.853	0.784, 4.380	0.160

Relative risks (RR) and 95% CI were computed from multivariate negative binomial regression models.



	Underweight	Normal weight	Overweight	Obesity	p-value
All SLE patients, n	**11**	**46**	**35**	**20**	
Presence of carotid plaques, n (%)	5 (45.5)	8 (17.4)	18 (51.4)	3 (15.0)	0.002
Plaque number, mean ± SD	0.91 ± 1.04	0.33 ± 0.76	0.86 ± 0.97	0.20 ± 0.52	0.003
cIMT (mm), median (IQR)	0.54 (0.07)	0.54 (0.11)	0.60 (0.21)	0.61 (0.11)	0.001
SLEDAI score, mean ± SD	2.91 ± 2.02	2.43 ± 2.45	1.66 ± 2.74	3.60 ± 3.39	0.009
Patients without CVD, n	**9**	**43**	**27**	**17**	
Presence of carotid plaques, n (%)	3 (33.3)	8 (18.6)	13 (48.1)	2 (11.8)	0.020
Plaque number, mean ± SD	0.67 ± 1.00	.0.35 ± 0.78	0.85 ± 1.02	0.18 ± 0.52	0.020
cIMT (mm), median (IQR)	0.54 (0.11)	0.54 (0.07)	0.59 (0.15)	0.61 (0.08)	0.005
SLEDAI score, mean ± SD	3.00 ± 2.12	2.44 ± 2.50	1.70 ± 2.55	3.88 ± 3.55	0.003