

Carotid artery atherosclerosis and ECG changes in patients with systemic lupus erythematosus: relation to disease activity and severity

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Aim

This study aimed to detect atherosclerotic changes in the carotid arteries of systemic lupus erythematosus (SLE) patients as an indicator of cardiovascular risk factors and to correlate the findings with disease severity and activity parameters as well as to study specific ECG changes in these patients to elucidate possible associations between these variables.

Patients and methods

This study included 30 SLE patients who met the Systemic Lupus International Collaborating Clinics (SLICC) criteria (group I), 30 rheumatoid arthritis (RA) patients diagnosed according to the American College of Rheumatology/European league against rheumatism (EULAR) 2010 criteria (group II), and 30 apparently healthy volunteers age and sex matched to the SLE patients' group (group III). All patients were subjected to full history taking, thorough clinical examination, assessment of disease activity using the Systemic Lupus Erythematosus Disease Activity Index (2K) score and assessment of damage by the SLICC/American College of Rheumatology Damage Index (SDI). Laboratory investigations included: complete blood count, erythrocyte sedimentation rate, lipid profile, immunological profile (antinuclear antibodies, anti-double-stranded DNA antibody, anticardiolipin antibody, and complements C3 and C4). The right common carotid artery was scanned by ultrasound and the average of carotid intima media thickness (CIMT) was calculated (mean of four readings) for all participants participating in the study. ECG was also done for all participants.

Results

The mean CIMT was higher in RA patients (0.71 ± 0.194 mm) with a nonsignificant difference compared with SLE patients (0.68 ± 0.197 mm) and a high statistically significant difference ($P < 0.001$) compared with healthy controls (0.34 ± 0.09 mm). There was no statistically significant correlation of the mean CIMT (mm) with SLICC damage index ($P = 0.09$) and disease activity score ($P > 0.05$). Abnormal ECG findings were observed in 3/30 SLE patients (10%), 10/30 RA patients (33.3%), and one/30 healthy control (3.3%), with statistically significant difference ($P < 0.03$) among groups. The presence or absence of abnormal ECG findings showed statistically insignificant differences regarding patients' disease activity and mean CIMT.

Conclusion

Although ECG changes were present in 10% of our SLE patients, association of specific ECG changes could not be confirmed. A greater prevalence of increased CIMT was observed in SLE patients, emphasizing the important role of this disease in the development of premature atherosclerosis which did not correlate with disease activity or severity parameters.

Keywords:

carotid artery atherosclerosis, ECG, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by autoantibody production and variable organ system manifestations, associated with increased risk of cardiovascular disease (CVD) [1]. SLE can affect any layer of the heart and cause endocarditis, myocarditis, and pericarditis which are generally reflected by symptoms and functional

disability [2]. Despite improvements in survival in the past decades, mortality due to CVD in SLE remains unchanged [3].

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SLE disease is an independent risk factor for CVD [4]. This makes traditional CV risk stratification scores developed for the general population less accessible in identifying patients with SLE at high risk for CVD. Consequently, there is a growing interest in improving CV risk stratification in SLE [5].

Subclinical atherosclerosis can be detected using several modalities, such as carotid intima media thickness (CIMT), flow-mediated dilation, coronary artery calcification by computed tomography scan, and myocardial perfusion using single-photon emission computed tomography [6]. CIMT assessed by B-mode ultrasound is a simple and noninvasive inexpensive tool that can be used to identify subclinical atherosclerotic disease; it is an independent predictor of future CV risk [7].

ECG is a useful universally available noninvasive inexpensive tool. Screening for resting ECG abnormalities in asymptomatic adults found that resting ECG serves as predictors of CV events and might help better guide use of risk-reduction therapies [8].

Aim

This study aimed to detect atherosclerotic changes in the carotid arteries of SLE patients as an indicator of CV risk factors and to correlate the findings with disease activity and severity parameters as well as to study specific ECG changes in these patients to elucidate possible associations between these variables.

Patients and methods

This study included:

Group I: 30 SLE patients who met the Systemic Lupus International Collaborative Clinics (SLICC) SLE Criteria [9].

Group II: 30 age-matched and sex-matched rheumatoid arthritis (RA) control patients diagnosed according to the American College of Rheumatology/EULAR 2010 criteria [10].

Group III: 30 age-matched and sex-matched apparently healthy control volunteers.

All patients were selected from the inpatients' and the outpatient's clinic of the Rheumatology, Rehabilitation and Physical Medicine Department, Benha University Hospitals. Controls were recruited from the hospital personnel and relatives of other patients.

The study was conducted according to the Helsinki Declaration and approved by the ethics committee of Benha Faculty of Medicine. An informed written consent was obtained from all the patients and control groups prior to the study.

Patients and controls were excluded from the study if their age is less than 16 years, had diabetes mellitus, hyperlipidemia on statins, hypertension, BMI greater than 25, smoking, previous history of CV events, and other autoimmune or inflammatory diseases.

All SLE patients were subjected to full medical history taking and thorough clinical examination. The SLE Disease Activity Index 2000 (SLEDAI 2k) [11] and the SLICC/American College of Rheumatology Damage Index (DI) [12] were used to assess disease activity and damage, respectively.

Laboratory investigations included complete blood count, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein, antinuclear antibodies, C3, C4, immunoglobulin G (IgG) antibodies to dsDNA, IgG/IgM anticardiolipin antibodies, complete urine analysis, renal function tests, 24 h proteins in urine, and fasting blood glucose. Total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were evaluated in blood samples taken in the morning after 14 h of fasting using standard enzymatic methods with an autoanalyzer.

Measurement of the CIMT by carotid ultrasound scan and ECG for patients and healthy controls were done by an experienced cardiologist who is one of the authors of this work.

Ultrasonographic study

Ultrasonography was performed with a GE Vivid 7 system (GE Healthcare, Milwaukee, WI) equipped with a 13 MHz linear array imaging probe. The right common carotid artery was examined with the patient lying supine, the head directed away from the side of examination, and the neck extended slightly. The transducer is manipulated so that the near and far walls of the common carotid artery are parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 1 cm proximal to the carotid bifurcation was identified, and the intima media thickness of the far wall was evaluated as the distance between the lumen-intima interface and the media-adventitia interface. The CIMT measurement is obtained from four contiguous sites at 1 mm intervals, and the average

of the four measurements is used for the analyses. The performing investigator was blinded to all clinical data. Upper normal average intima media thickness is estimated to be up to 0.8 mm with plaque defined as a thickness greater than 1.5 mm as measured from the media–adventia interface to the intima–lumen interface [13].

ECG

A standard digitally recorded 12-lead resting supine ECG was performed in the Cardiology Department, Benha University Hospitals. It was performed by Nihon Kohden's Cardiofax C ECG (Nihon Kohden's, Japan). ECG-CVD were considered if there was one or more of the following four elements (ECG-4): ST-segment and/or T-wave abnormalities, left ventricular hypertrophy (LVH), left axis deviation (LAD), left bundle branch block (LBBB), and right bundle branch block (RBBB). ECG was interpreted by one of the authors who was blinded to the patients' data.

Statistical analysis

Data were tabulated, coded, and then analyzed using the computer program SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, Illinois, USA) version 22. Descriptive statistics were calculated for the data in the form of mean±SD and number and percentage. Analysis of variance test was used to compare between more than two groups of numerical (parametric) data, for continuous nonparametric data. Kruskal–Wallis test was used for intergroup analysis; post-hoc test (LSD, Least significant difference) was used to compare between every two groups; and Student's *t*-test was used to compare between two groups of numerical (parametric) data. Mann–Whitney test was used for intergroup analysis; χ^2 -test was used for comparison of categorical data. Correlation coefficient (*r*) was used to detect the association between different variables. A *P* value less than 0.05 was considered statistically significant and a *P* value less than 0.0001 was considered highly significant in all analyses.

Results

This study included 30 SLE patients, 28 (93.3%) women and two (6.7%) men, whose ages ranged between 21 and 53 years (mean±SD 34.7±7.9 years), and their disease duration ranged between 2 months and 37 years (mean±SD 8.4±8.5 years). There were 30 RA control patients, 27 (90%) women and three (10%) men whose ages ranged between 20 and 50 years (mean±SD 35.9±6.8 years) and their disease duration ranged between 1 and 26 years (mean±SD 7.6±7.2 years) and 30 apparently healthy control volunteers, 26 (86.6%) women and four (13.3%) men whose ages ranged between 20 and 59 years (mean±SD 34.9±8.8 years). All three groups had nonsignificantly different ages (*P*>0.05) and sex (*P*>0.05) compared with each other.

Clinical features of SLE patients were malar rash in 25 (83.4%) patients, photosensitivity in 18 (60%) patients, oral ulcers in 20 (66.7%) patients, arthritis and/or arthralgia in all of the patients (100%), pulmonary manifestations in the form of pleuritis and/or effusion in 10 (33.3%) patients, neurological manifestations in the form of headache, seizures were found in three (10%) patients, 23 (76.7%) patients had lupus nephritis based on the presence of proteinuria, active urine sedimentation, or biopsy-proven renal disease.

CIMT findings in the studied groups

SLE patients had a CIMT that ranged from 0.25 to 1.1 mm thickness (mean±SD 0.68±0.197 mm), only 10 out of 30 SLE cases showed an increased CIMT of above 0.8 mm, while RA patients had a CIMT ranged from 0.39 to 1.2 mm thickness (mean±SD 0.71±0.194 mm), only 12 out of 30 RA cases showed an increased CIMT of above 0.8 mm (Table 1).

SLE patients had a nonsignificant difference compared with RA controls (*P*>0.05) and a significant difference compared with healthy controls (*P*<0.05).

There were no statistically significant correlations of mean CIMT values with patients' ages (*r*=0.18;

Table 1 Comparison among systemic lupus erythematosus patients and the control groups regarding the mean carotid intima media thickness

Variables	SLE patients (<i>n</i> =30) (mean±SD)	RA controls (<i>n</i> =30) (mean±SD)	Healthy controls (<i>n</i> =30) (mean±SD)	<i>F</i> test	<i>P</i> value	Post-hoc analysis
CIMT (mm)	0.68±0.197	0.71±0.194	0.34±0.09	44.2	<0.001**	<i>P</i> ₁ >0.05 <i>P</i> ₂ <0.05* <i>P</i> ₃ <0.05*

CIMT, carotid intima media thickness; *P*₁, between SLE and RA; *P*₂, between SLE and healthy control; *P*₃, between RA and healthy control; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. ***P*<0.001, highly significant. **P*<0.05, significant. *P*>0.05, nonsignificant.

$P=0.34$), BMI ($r=-0.01$; $P=0.94$), and disease duration ($r=0.23$; $P=0.23$).

There were no correlation between mean CIMT and SLE patients' sex ($P=0.9$), family history of premature CVD, positive anti-dsDNA ($P=0.9$), or positive CRP ($P=0.5$).

There were no statistically significant correlations of mean CIMT values with TC ($r=0.08$; $P=0.68$), HDL ($r=-0.33$; $P=0.08$), and LDL ($r=0.07$; $P=0.73$), while there was a statistically significant correlation with the level of triglycerides ($r=0.52$; $P=0.00$). Other laboratory parameters also showed nonsignificant correlations (hemoglobin%, red blood cells, white blood cells, platelets, ESR, serum urea, serum creatinine, 24h protein in urine, C3, and C4).

Table 2 Comparisons among the studied groups regarding ECG findings

Variables	SLE (n.=30) [n (%)]	RA controls (n=30) [n (%)]	Healthy controls (n=30) [n (%)]	Stat- test	P value
Abnormal ECG findings	3 (10)	10 (33.3)	1 (3.3)	11.4	0.003*
Normal ECG findings	27 (90)	20 (66.6)	29 (96.6)		

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

There were no statistically significant differences of mean CIMT among SLE with different disease activity scores ($P>0.05$) as well as a nonsignificant correlation between mean CIMT and SLICC damage index ($r=0.31$, $P=0.09$).

There were no statistically significant ($P>0.05$) correlations of mean CIMT regarding the duration of drug used (prednisone, chloroquine, and azathioprine).

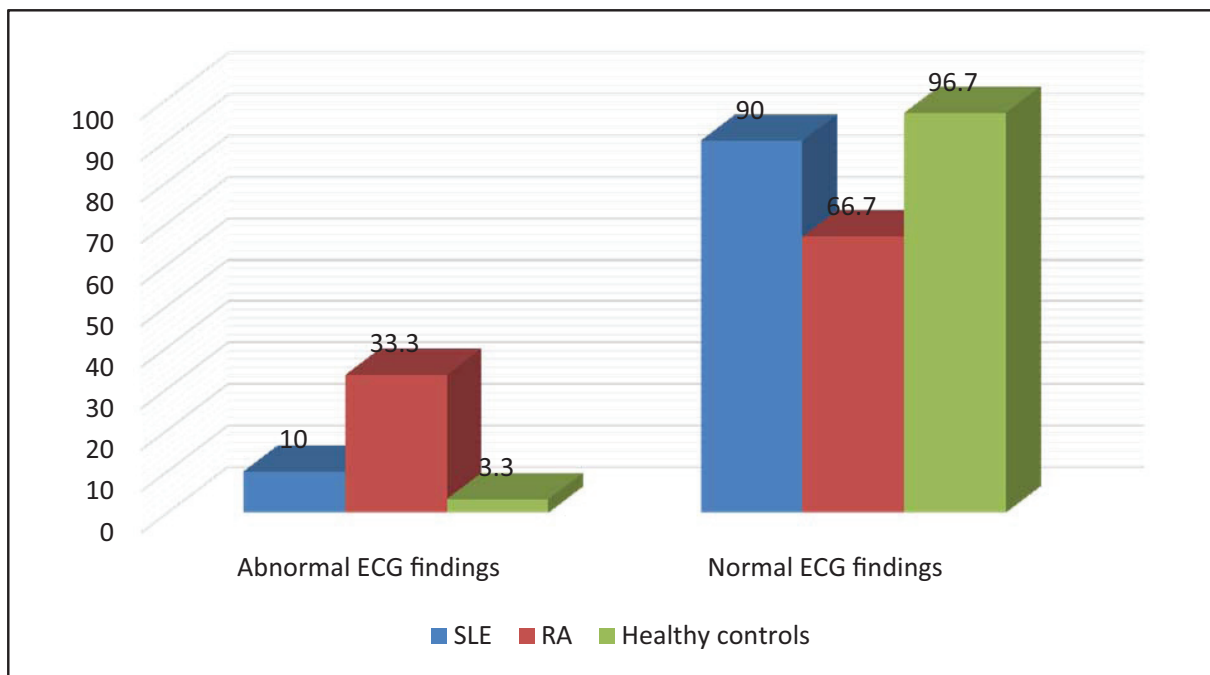
ECG findings in the studied groups

Two/30 SLE patients (6.7%) had ST-segment abnormalities, one (3.3%) patient had RBBB the remaining 27 (90%) patients had a normal ECG study. None of the SLE patients had left ventriculaLVH, LAD or the Q-wave, while 7/30 RA patients (23.3%) had ST-segment abnormalities, three (10%) patients had LVH; the remaining 20 (66.6%) patients had a normal ECG study. None of the RA patients had LBBB, RBBB, LAD, or the Q-wave (Table 2 and Fig. 1).

ECG abnormalities in SLE patients were nonsignificantly different compared with healthy controls ($P=0.028$) and were significantly different compared with RA controls who had the highest frequencies of ECG abnormalities.

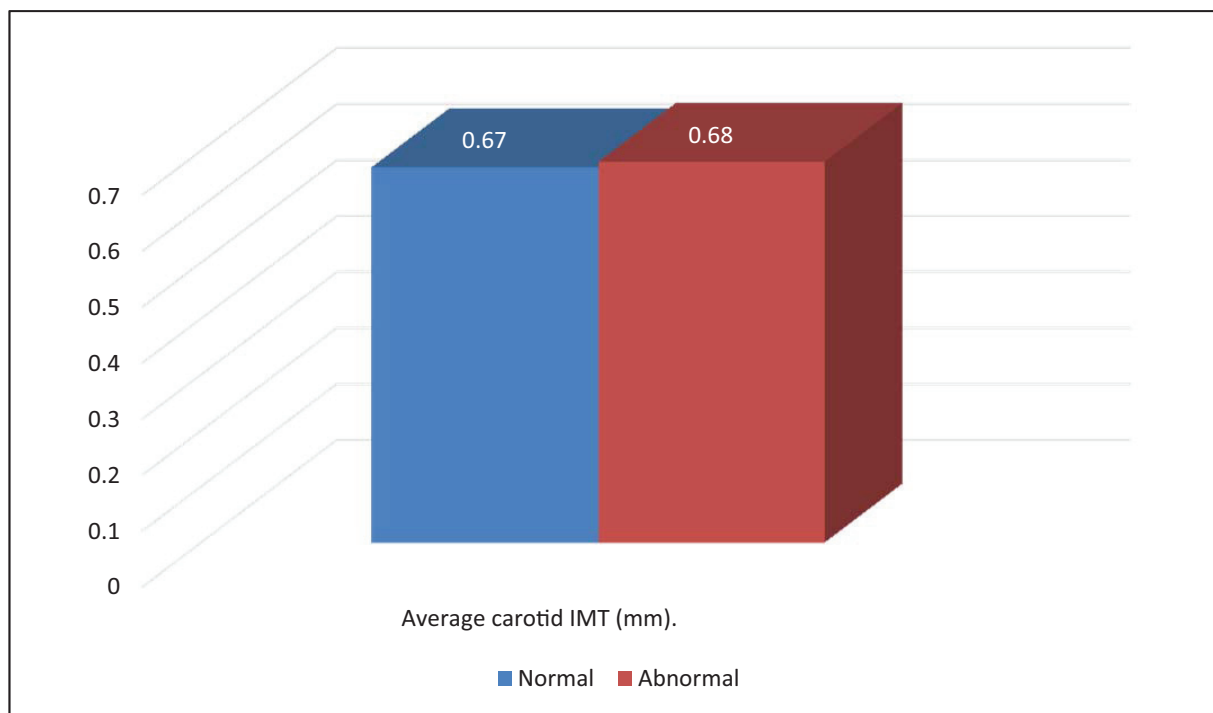
Comparative studies of ECG findings in the SLE group regarding patients age (years), BMI (kg/m^2),

Figure 1



Comparisons among the studied groups regarding ECG findings.

Figure 2



Comparison of mean carotid intima media thickness of systemic lupus erythematosus patients regarding ECG findings ($P=0.9$).

disease duration, disease activity, and mean CIMT revealed statistically insignificant differences ($P=0.05$).

Comparisons of ECG findings regarding laboratory data of SLE patients revealed nonsignificant differences except for ESR ($P=0.01$).

There were nonsignificant differences ($P>0.05$) regarding the occurrence of normal or abnormal ECG changes in relation to the durations of all the medications used.

There was no significant difference of mean CIMT between patients with and without ECG changes (Fig. 2).

Discussion

SLE is associated with an increased risk of CVD. Measurement of the CIMT is such a marker that can be used to diagnose subclinical atherosclerotic disease. The ECG is a noninvasive screening tool for the evaluation and identification of patients at increased risk for CV events with a relatively minimal cost burden. Dyslipidemia is defined as any alteration in the basic lipid profile that affects about one-third of SLE patients at the time of diagnosis and almost 60% after 3 years [14].

Esdaile *et al.* [15] reported that the excess of CV events in SLE cannot be explained only by the traditional risk factors but also arises from the underlying disease and/or its treatment.

Regarding our results, there was a statistically significant difference ($P<0.05$) between the mean CIMT of SLE patients and the healthy control group (0.68 ± 0.197 vs. 0.34 ± 0.09) respectively, while there was a nonstatistically significant difference ($P>0.05$) between the mean CIMT of the SLE patients' group and the RA control group (0.68 ± 0.197 vs. 0.71 ± 0.194), respectively. These results are in agreement with those of de Leeuw *et al.* [16], El Saadany *et al.* [17], and Uslu *et al.* [18]. Inflammation plays a role in the development of the atherosclerotic lesion, interaction between traditional risk factors, antibody-mediated vascular injury, and immune dysregulation from the underlying disease, all play vital roles in endothelial dysfunction which accelerates the atherosclerotic development in SLE [19].

We also found that, there was a statistically significant correlation of mean CIMT values with the level of triglycerides ($r=0.52$; $P=0.004$), nonstatistically significant correlations ($P>0.05$) with TC ($r=0.08$; $P=0.68$), HDL ($r=-0.33$; $P=0.08$) and LDL ($r=0.07$; $P=0.73$). This is in agreement with the results of Sozeri *et al.* [20] and Kiani *et al.* [21].

Nikpour *et al.* [14] demonstrated that lipid values may change over time, reflecting changes in disease activity and therapy with antimalarials which exhibit a favorable effect on the lipid profile.

In this study, there were insignificant correlations ($P>0.05$) of mean CIMT values with patients' ages ($r=0.18$), sex ($P=0.9$), lupus disease duration ($r=0.23$), and patients family history of premature coronary artery disease ($P=0.5$) in first-degree relatives before the age of 65 years for women and 55 years for men.

Khairy *et al.* [22] found that SLE cases with a history of CVD had a significantly increased CIMT compared with both those without CVD history or healthy controls ($P<0.001$). They explained in their study that there was a significant difference regarding CRP and ESR between the two SLE groups. They also found a significant difference regarding levels of both lupus anticoagulants ($P=0.01$), ACL antibodies ($P=0.006$), higher cumulative prednisone dose ($P=0.4$), and SLEDAI score (0.001) compared with SLE controls (without CVD).

Insignificant correlations of the disease activity score (SLEDAI 2k) and SLICC damage index were found among SLE patients regarding the mean CIMT ($P=0.9$, 0.09, respectively). All correlations of the laboratory parameters (hemoglobin, red blood cells, white blood cells, platelets, ESR, serum urea, serum creatinine, 24 h urine protein, C3 and C4) as well as the duration of drugs used with CIMT in the SLE patients' group I were nonsignificant ($P>0.05$). This was in agreement with Falaschi *et al.* [23] and Kiani *et al.* [21] studies; meanwhile, it did not coincide with both Kisiel *et al.* [24] and Hassan *et al.* [25]. This could be explained by a small number of SLE patients in our study and 93.3% of our cases were women which had milder disease severity than men. Al Rayes *et al.* [26] reported that ECG-CVD abnormalities (ECG-CVD) are predictive of subsequent CVD events in the general population and that SLE patients are vulnerable to CVD.

This work showed a total of 3/30 (10%) SLE patients having abnormal ECG findings compared with 10/30 (33.3%) RA patients and one (3.3%) of the normal control group, with a statistically significant difference ($P<0.003$). However, Bourré-Tessier *et al.* [3] and Myung *et al.* [27] detected a higher prevalence of resting ECG abnormalities in their SLE patients (58.2 and 57.4%, respectively). This may be explained by the difference in sample size and lack of hospital database as we investigated only 30 SLE patients in our

study, but they collected 558 SLE patients from 2011 to 2015 as a part of their regular databank protocol.

In our study, a higher prevalence of nonspecific ST-T abnormalities occurred in 6/10 (23.3%) of RA patients compared with 2/3 (6.7%) of SLE patients. This was not in agreement with Geraldino-Pardilla *et al.* [6] who observed that SLE disease has a higher prevalence of nonspecific ST-T abnormalities (56 vs. 17%; $P<0.0001$) compared with RA, despite the older age, in a higher percentage of men in the RA group. This may be explained by the difference in sample size and races, as our study included only Egyptian patients.

Comparative studies of ECG findings among SLE patients regarding patients' data, disease activity scores, and average CIMT measurements revealed statistically insignificant differences ($P=0.05$) which are in accordance with Geraldino-Pardilla *et al.* [6] results. However, Al Rayes *et al.* [26] reported a higher prevalence of ECG-CVD in patients with a longer SLE disease duration, increased patients' ages, active SLE disease, and damage while treatment of hyperlipidemia was protective against such events.

Conclusion

Ten out of 30 SLE (33.3%) cases showed an increased CIMT of above 0.8 mm of CIMT, emphasizing the important role of this disease in the development of premature atherosclerosis. ECG changes were present in 10% of our SLE patients; meanwhile, the association of specific ECG changes could not be confirmed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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