

## Role of Nailfold Capillaroscopy as A Method of Detection of Atherosclerosis in Systemic Lupus Erythematosus Patients

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### ABSTRACT

**Background:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with increased risk of atherosclerosis. Despite the relative youth of lupus patients, they have risk for the development of premature cardiovascular atherosclerotic diseases. **Objective:** This work aimed to study the detection of atherosclerosis and the cardiovascular risk in SLE patients by nail fold capillaroscopy and the intima media thickness of the carotid artery.

**Patients and methods:** This was a cross sectional study included 60 SLE patients. Patients were collected from the Outpatient Clinic and Inpatient of Internal Medicine and Rheumatology Departments within 6 months.

**Results:** 22 patients (36.7%) had atherosclerosis, with higher SLE disease activity index (SLEDAI) score (p 0.002). 45.5% of them had severe disease activity and 54.5% had moderate disease activity. Atherosclerotic patients had statistically significant lower capillary density (P 0.001), higher capillary length (P 0.008), capillary width (P < 0.001) and arterial limb diameter (P < 0.001) with higher prevalence of tortuous (P= 0.022), meandering (p=0.014) and disorganized capillaries (P= 0.008). There was statistically significant positive correlation between Intima media thickness (IMT) and disease duration, SLEDAI score, capillary width and arterial limb diameter, while there was statistically significant negative correlation with capillary density. The Arterial limb diameter had highest diagnostic performance in diagnosing atherosclerosis.

**Conclusion:** Atherosclerosis is common in SLE & is associated with higher diseases activity. By capillaroscopy, lower density, longer, wider and disorganized capillaries and tortuous & meandering capillaries were associated with the presence of atherosclerosis.

**Key words:** Capillaroscopy, atherosclerosis, SLE.

### INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease usually affects women at reproductive age<sup>1</sup>. Atherosclerosis is an inflammatory process, which affects intima of arteries<sup>2</sup>. Inflammation is involved in the pathogenesis of both lupus and atherogenesis. Endothelial injury caused by several factors including autoantibody production, impaired immune complex clearance and complement activation, which are associated with the pathogenesis of both SLE and coronary artery disease<sup>3</sup>. Quantification of the carotid artery intima-media thickness using ultrasonography has been used to diagnose atherosclerosis<sup>4</sup>. Nail fold capillaroscopy (NFC) is a simple technique, which is useful to detect atherosclerosis and microcirculation<sup>5</sup>. Different abnormal NFC changes are quite common among patients with SLE, and nail fold capillaroscopy is an effective method to monitor such changes. Treatment strategies may change in the different patterns of nail fold capillaroscopy<sup>6</sup>.

NFC can be beneficial in the disease diagnostic process, and the extent of microvascular involvement in SLE may be reflected by the abnormal changes in nail fold capillaroscopy. Severe or moderate pathological changes under NFC were found in all reported SLE patients with internal organ manifestations<sup>7</sup>. This work aimed to study the detection of atherosclerosis and the cardiovascular risk

in SLE patients by nail fold capillaroscopy and the intima media thickness of the carotid artery.

### PATIENTS AND METHODS

This was a cross sectional study included 60 SLE patients. Patients were collected from the Outpatient Clinic and Inpatient of Internal Medicine and Rheumatology departments within 6 months.

**Inclusion criteria:** SLE patients fulfilling the American College of Rheumatology and European League against Rheumatism (ACR / EULAR) 2012 classification criteria for SLE<sup>8</sup>.

**Exclusion criteria:** Patients with diabetes mellitus, hypertension, obese patients "BMI more than 30" and patients with other connective tissue diseases were excluded from the study.

**Ethical consideration:** The study was approved by Local Research Ethical Committee of Ain Shams University and conforms to the provisions of the Declaration of Helsinki in 1995. Informed consent from all patients was obtained after explaining the aim of the work and study design.

Demographic data including age, sex and disease duration, clinical manifestations including musculoskeletal, constitutional, renal, neurological, hematological, mucocutaneous, cardiovascular,



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pulmonary, and gastrointestinal and drugs used for treatment including steroids, hydroxychloroquine and immunosuppressive drugs were carefully recorded. Disease activity was assessed using SLEDAI score <sup>9</sup>. Activity categories were defined as follow: Score 0 considered non active, score 1-5 considered as mild activity, score 6-10 considered as moderate activity and score 11-19 considered as high activity and score 20 or more considered asd very high activity<sup>9</sup>.

**Laboratory investigations:** including complete blood picture (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), kidney function test, liver enzymes, lipid profile, antinuclear antibody (ANA), anti-double stranded DNA antibody (anti ds-DNA), antiphospholipid antibodies, complement 3 and complement 4.

**Radiological investigations:** Including nail fold capillary microscopy (NFC) and carotid duplex were done to all included patients.

NFC was carried out using a videocapillaroscopy with a probe (magnification ×200). Examination was done for the eight fingers thumb was excluded. All the images were registered and collected using a dedicated software system (Blu Vision). NFC was performed according to the standard method using high magnification videocapillaroscopy, at room temperature using light olive oil as lubricants <sup>10</sup>.

The following parameters were considered, comment on the shape of the capillaries (normal hairpin or abnormal shape eg. meandering, corkscrew or tortuous capillaries), the diameter of the capillaries is determined (dilated loops considered if loop diameter is more than 20 µm and mega capillaries if ≥ 50 µm) and capillary length (normal or elongated ≥ 300µm). Comment on mean capillary density (low capillary density defined as number of capillaries below 7 per linear mm), avascular area (inter capillary distance ≥ 500 µm) and comment on the presence or absence of microhemorrhage was done <sup>10</sup>. Patients were also subjected for carotid artery duplex to detect the presence or absence of increased carotid intima –media thickness (IMT) through measuring IMT by B-mode ultrasound using Toshiba Xario (USA) using 7.5 MHs probe. For each segment, the maximal value of IMT is selected and the final IMT considered is the average of IMT values at the 12 examined sites. Patients with IMT < 1 mm were considered non-atherosclerotic, while those with IMT >1 mm were considered atherosclerotic <sup>4</sup>.

**Statistical analysis**

The Statistical package for Social Science (SPSS version 20) was used. Data were presented and suitable analysis was performed. Unpaired student T-test was used to compare between two independent groups regarding quantitative data. Chi-square was used to compare qualitative variables. P value ≤ 0.05 was considered

significant. Pearson's correlation coefficient (r) test was used for correlating data.

**RESULTS**

Among the studied 60 patients 58 (96.7%) were females and 2 (3.3%) were males. They had a mean age of 42.8 ± 2.2 years and a mean disease duration of 6.0 ± 2.2 years (Table 1).

**Table (1):** Descriptive data of the studied patients

Characteristics		Mean ± SD
Age/ years		42.8 ± 5.4
Disease duration/ years		6.0± 3.3
sex		N
	male	2
	female	58
SLEDAI score		17.6±1.4
		N
Severity	Mild	20
	Moderate	26
	Severe	14
Triglycerides (mg/dL)		140.3±14.8
LDL (mg/dL)		131.5±14.2
HDL (mg/dL)		59.2±10.6
ESR (mg/dL)		52.3±9.3
CRP (mg/dL)		23.2±7.0
C3 (mg/dL)		58.8±10.6
C4 (mg/dL)		14.1±3.0
		N
Anti dsDNA	Positive	42
	Negative	18
Antiphospholipid	Positive	0
	Negative	60
Capillary Density (7.3–10.3 mm)		8.9±1.0
Capillary Length (92.0–295.0 µm)		141.5±12.7
Width diameter (27.0–59.5 µm)		26.5±4.3
Arterial loop diameter (7.0–17.0 µm)		14.8±3.9
		N
Shape	Meandering	32
	Tortuous	28
	Corkscrew	10
	Bushy	4
	Hairpin	4
Hemorrhage		8
Subpapillary Plexus		28
Avascular areas		0
Distribution	Disorganization	36
	Organization	24

According to the intima media thickness assessed by carotid duplex, patients were classified into

atherosclerotic group [22 patients (36.7%)] and non-atherosclerotic group [38 (63.3%)].

**Table (2):** Comparison between both groups regarding demographic data

Variables		Atherosclerotic (N=22)	Non-atherosclerotic (N=38)	Test value	P-value	Sig.
Age (years)	Mean±SD	46.0±5.3	41.0±4.7	t=	3.098	0.010*
	Range	39.0–57.0	34.0–49.0			
Age of disease onset (years)	Mean±SD	38.0±2.0	36.2±2.1	t=	2.696	0.022*
	Range	35.0–42.0	33.0–40.0			
Disease duration (years)	Mean±SD	8.0±3.4	4.8±2.7	t=	3.218	0.008*
	Range	4.0–15.0	1.0–9.0			
Sex	Male	0 (0.0%)	2 (5.3%)	$\chi^2=$	0.689	0.780
	Female	22 (100.0%)	36 (94.7%)			

On comparing both groups, atherosclerotic patients were statistically significantly older (p=0.012) with statistically significant longer disease duration (p=0.009) (Table 2).

Atherosclerotic patients had statistically significant higher SLEDAI score (p 0.002), higher frequency of moderate (P 0.001) and severe (P 0.009) disease activity (Table 3).

**Table (3):** Comparison between both groups regarding disease activity

Variables		Atherosclerotic (N=22)	Non-atherosclerotic (N=38)	Test value	P-value	Sig.
SLEDAI score	Mean ±SD	11.6±3.1	7.0±3.8	t=	3.966	0.002*
	Range	7.0–17.0	4.0–15.0			
Severity	Mild	0 (0.0%)	20 (52.7%)	$\chi^2=$	11.426	0.002*
	Moderate	12 (54.5%)	14 (36.8%)			0.001*
	Severe	10 (45.5%)	4 (10.5%)			0.007*

Also, there was statistically significant difference between atherosclerotic and non-atherosclerotic SLE patients as regards the frequency of arthritis ( P 0.007) and nephritis ( P 0.007) being higher in the atherosclerotic patients. Moreover, atherosclerotic patients had statistically significant higher doses of steroids (P < 0.001) (Table 4).

**Table (4):** Comparison between both groups regarding clinical manifestations and drug intake

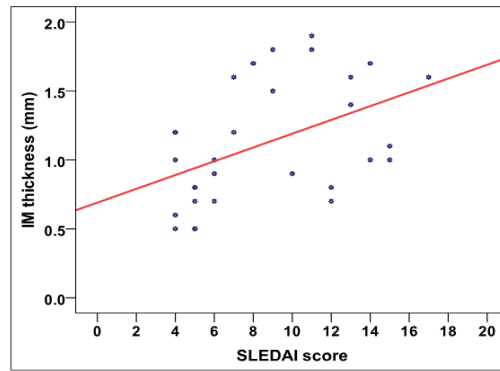
Parameters	Atherosclerosis (n=22)	Non atherosclerotic (n=38)	Test	p-value
Corticosteroid (mg)	31.29±5.32	10.43±1.77	t=22.251	<0.001**
Immunosuppressive	13 (59.1%)	17 (44.7%)	$\chi^2=0.651$	0.419
Hydroxychloroquine	5 (22.7%)	24 (63.2%)	$\chi^2=7.602$	0.006*
Arthritis	15 (68.2%)	11 (28.9%)	$\chi^2=7.237$	0.007*
rash	7 (31.8%)	11 (28.9%)	$\chi^2=0.003$	0.995
Nephritis	13 (59.1%)	8 (21.1%)	$\chi^2=7.249$	0.007*
Serositis	4 (18.2%)	7 (18.4%)	$\chi^2=0.107$	0.744
CNS	2 (9.1%)	3 (7.9%)	$\chi^2=0.104$	0.747

Regarding nail fold capillaroscopic findings, atherosclerotic patients showed statistically significant higher prevalence of longer capillaries (p=0.009), lower capillary density (p=0.001), wider capillary diameter (p=0.002) and larger arterial limb diameter (p=0.001). In addition, meandering, tortuous and disorganization were significantly more frequent in atherosclerosis cases (P 0.014), (P 0.022), (P 0.008) respectively (Table 5)

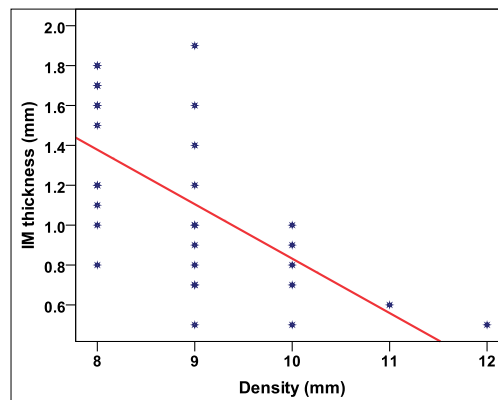
**Table (5):** Comparison between both groups regarding laboratory data and nail fold capillaroscopic findings

Variables		Atherosclerosis (N=22)	No atherosclerosis (N=38)	Test value	P-value	Sig.
Cholesterol (mg/dL)	Mean±SD	222.3±24.1	213.4±24.7	t=	^	NS
	Range	183.0–257.0	174.0–264.0	1.097	0.296	
Triglycerides (mg/dL)	Mean±SD	142.6±14.5	138.9±15.2	t=	^	NS
	Range	117.0–163.0	115.0–173.0	0.749	0.442	
LDL (mg/dL)	Mean±SD	140.4±13.1	126.8±12.8	t=	^	S
	Range	115.0–157.0	104.0–156.0	3.203	<b>0.009*</b>	
HDL (mg/dL)	Mean±SD	57.4±11.0	60.2±10.5	t=	^	NS
	Range	42.0–78.0	41.0–84.0	-0.810	0.414	
ESR (mg/dL)	Mean±SD	56.4±10.2	49.2±8.4	t=	^	S
	Range	42.0–72.0	41.0–76.0	2.884	<b>0.031*</b>	
CRP (mg/dL)	Mean±SD	24.8±6.4	22.3±5.3	t=	^	NS
C3 (mg/dL)	Mean±SD	56.6±10.5	60.1±10.6	t=	^	NS
	Range	39.0–78.0	39.0–79.0	-0.978	0.342	
C4 (mg/dL)	Mean±SD	13.6±2.7	14.4±3.2	t=	^	NS
	Range	9.0–19.0	8.0–22.0	-0.796	0.421	
Anti dsDNA	Positive	16 (72.7%)	26 (68.4%)	$\chi^2=$ 0.689	0.683	NS
	Negative	6 (27.3%)	12 (31.6%)			
Capillary Density (mm)	Mean±SD	8.3±0.5	9.3±1.1	t=	<b>0.001*</b>	S
	Range	8.0–9.0	8.0–12.0	4.278		
Capillary Length (µm)	Mean±SD	149.2±15.3	137.0±8.6	t=	<b>0.008*</b>	S
	Range	111.0–173.0	124.0–157.0	3.230		
Width diameter (µm)	Mean±SD	31.0±5.9	22.8±4.2	t=	<	S
	Range	19.0–37.0	15.0–28.0	6.582	<b>0.001*</b>	
Arterial loop diameter	Mean±SD	18.7±2.2	12.6±2.7	t= 7.304	<	S
	Range	14.0–22.0(µm)	9.0–16.0(µm)		<b>0.001*</b>	
Shapes	Meandering	18 (81.8%)	14 (36.8%)	$\chi^2=$ 6.511	<b>0.014*</b>	S
	Tortuous	16 (72.7%)	12 (31.6%)	$\chi^2=$ 5.450	<b>0.022*</b>	S
	Corkscrew	6 (27.3%)	4 (10.5%)	$\chi^2=$ 1.618	0.201	NS
	Bushy	2 (9.1%)	2 (5.3%)	$\chi^2=$ 0.189	0.582	NS
	Hairpin	0 (0.0%)	4 (10.5%)	$\chi^2=$ 1.427	0.225	NS
Haemorrhage		6 (27.3%)	2 (5.3%)	$\chi^2=$ 3.359	0.074	NS
Sub papillary plexus		10 (45.4%)	18 (47.3%)	$\chi^2=$ 3.359	0.074	NS
Distribution	Disorganization	20 (90.9%)	16 (42.1%)	$\chi^2=$ 7.951	<b>0.008*</b>	S
	Organization	4 (9.1%)	22 (57.9%)			

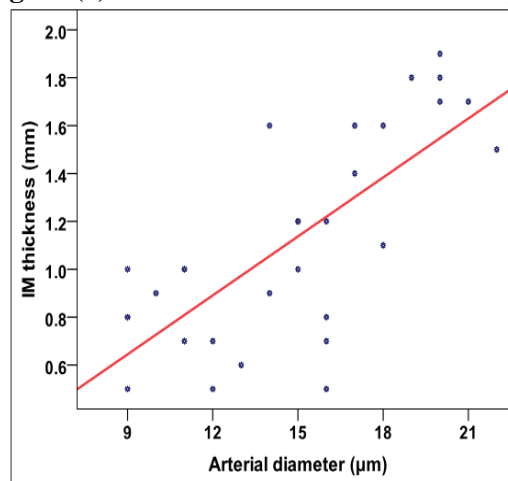
Correlating carotid IMT with capillaroscopic findings, disease activity and various laboratory data documented statistically significant positive correlation between IMT and age (  $r= 0.427$  , $P 0.037$ ), disease duration ( $r=0.484$ ,  $P 0.017$ ), SLEDAI score ( $r= 0.536$ ,  $P 0.008$ ), capillary width (  $r= 0.692$  , $P <0.001$ ) and arterial limb diameter ( $r= 0.846$ , $P <0.001$ ). While, there was statistically significant negative correlation with capillary density ( $r= -0.728$ ,  $P <0.001$ ) (Fig 1, 2, 3).



**Figure (1):** Correlation between IM thickness and SLEDAI score



**Figure (2):** Correlation between IMT and capillary density



**Figure (3):** correlation between IMT and arterial limb diameter

In addition, the arterial limb diameter found to has the highest diagnostic performance in diagnosing atherosclerosis. The arterial diameter  $\geq 17.0 \mu\text{m}$  had highest diagnostic characteristics in diagnosing atherosclerosis (Tables 6, 7).

**Table (6):** Diagnostic performance of nail fold capillaroscopy in diagnosing atherosclerosis

Factors	AUC	SE	P-value	95% CI	Cut off
Density	0.840	0.078	<b>0.002*</b>	0.840–0.078	$\geq 9.0$
Length	0.833	0.093	<b>0.003*</b>	0.833–0.093	$\geq 144.0$
Width	0.825	0.075	<b>0.003*</b>	0.825–0.075	$\geq 55.0$
Arterial diameter	0.964	0.037	<b>&lt;0.001*</b>	0.964–0.037	$\geq 17.0$

AUC: Area under curve, SE: Standard error, CI: Confidence interval, \*significant

**Table (7):** Diagnostic characteristics of nail fold capillaroscopy in diagnosing atherosclerosis

Characters	Density ≥9.0	Length ≥144.0	Width ≥55.0	Diameter ≥17.0	Meandering	Tortous
<b>Sensitivity</b>	100.0%	81.8%	54.5%	90.9%	81.8%	72.7%
<b>Specificity</b>	5.3%	84.2%	89.5%	100.0%	63.2%	68.4%
<b>DA</b>	40.0%	83.3%	76.7%	96.7%	70.0%	70.0%
<b>YI</b>	5.3%	66.0%	44.0%	<b>90.9%</b>	45.0%	41.1%
<b>PPV</b>	37.9%	75.0%	75.0%	100.0%	56.3%	57.1%
<b>NPV</b>	100.0%	88.9%	77.3%	95.0%	85.7%	81.3%
<b>LR+</b>	1.06	5.18	5.18	>100.0	2.22	2.30
<b>LR-</b>	0.00	0.22	0.51	0.09	0.29	0.40
<b>LR</b>	>100.0	24.00	10.20	>100.0	7.71	5.78
	<b>Corkscrew</b>	<b>Bushy</b>	<b>Enlargment</b>	<b>Hemorrhage</b>	<b>Plexus</b>	<b>Disorganization</b>
<b>Sensitivity</b>	27.3%	9.1%	36.4%	27.3%	9.1%	90.9%
<b>Specificity</b>	89.5%	94.7%	84.2%	94.7%	94.7%	57.9%
<b>DA</b>	66.7%	63.3%	66.7%	70.0%	63.3%	70.0%
<b>YI</b>	16.7%	3.8%	20.6%	22.0%	3.8%	48.8%
<b>PPV</b>	60.0%	50.0%	57.1%	75.0%	50.0%	55.6%
<b>NPV</b>	68.0%	64.3%	69.6%	69.2%	64.3%	91.7%
<b>LR+</b>	2.59	1.73	2.30	5.18	1.73	2.16
<b>LR-</b>	0.81	0.96	0.76	0.77	0.96	0.16
<b>LR</b>	3.19	1.80	3.05	6.75	1.80	13.75

YI: Youden's index, DA: Diagnostic accuracy, PPV: Positive Predictive value, NPV: Negative Predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, LR: Diagnostic odd ratio.

**DISCUSSION**

SLE is an autoimmune disease characterized by exacerbations and remissions. Autoantibody production and immune complex deposition leads to immunological self-tolerance breakdown, release inflammatory cytokines and activation of T cells<sup>11</sup>. The inflammatory mediators may contribute to the formation of atherosclerosis in SLE, which makes SLE a risk factor to atherosclerosis<sup>12</sup>.

Nail fold capillaroscopy (NFC) is a safe, non-invasive technique used to detect peripheral microangiopathy. It is also defined to have diagnostic and prognostic value. Microvascular involvement is an important feature in SLE. In patients with SLE, microvascular changes may be evaluated by NFC<sup>13</sup>. NFC may be used in personalized medicine as an adjunct in assessing SLE activity, which may help prognosticate risk of serious complications<sup>14</sup>.

This study included 60 patients; 58 patients were females and 2 males with a mean age of 42.8± 5.4. These results run in agreement with **Parks et al.**<sup>15</sup> who reported that SLE is more common in females than males.

Accelerated atherosclerosis is often considered a general feature of SLE and is, in similarity to the general population assumed to be the main cause of premature cardiovascular disease (CVD)<sup>16</sup>. In this study, 22 (36.7%) patients had atherosclerosis identified by increased intima media thickness. This comes in

agreement with **khairy et al.**<sup>17</sup> and **McMahon et al.**<sup>18</sup> as it concluded that SLE patients had significantly increased IMT compared to general population. In addition, **Gustafsson et al.**<sup>16</sup> concluded that atherosclerosis is common among SLE patients with a prevalence of 16-20%. Furthermore, in a study conducted by **Katz et al.**<sup>19</sup> comparing hospitalized lupus patients with age and sex matched non-SLE patients, they concluded that SLE was associated with more prevalence of atherosclerotic cardiovascular complications. Age play a very important risk factor for atherosclerosis<sup>19</sup>, in a study conducted by **Doria et al.**<sup>20</sup>, they reported that SLE patients with increased IMT were significantly older. This is in harmony with results of the current study as we found that atherosclerotic SLE patients were older in age.

As regards laboratory investigations in the present study, higher ESR was detected in atherosclerotic group in comparison to non-atherosclerotic. However, there was no difference regarding the rest of the C3, C4 and ds-DNA. This is consistent with **Gustafsson et al.**<sup>16</sup> who found no differences between lupus patients with carotid plaque and those without regarding ds DNA seropositivity; however, they detected higher level of C4 in patients with carotid plaque.

Although serum cholesterol and triglycerides were higher in the atherosclerotic than non-atherosclerotic patients but it did not reach the statistical significance. This disagrees with **khairy et al.**<sup>17</sup> who

stated that SLE patients with increased IMT had dyslipidemia with raised TG, LDL and low HDL level. That disagreement may be due to small sample size of our study.

SLE disease activity has been shown to be an independent predictor of organ damage and mortality, it is also considered as a lupus –specific risk factor for premature atherosclerosis<sup>18</sup>.

In the current study, the statistically significant higher frequency of arthritis and nephritis with higher doses of steroids in the atherosclerotic SLE patients compared to the non-atherosclerotic may reflect more severe disease and organ damage. In addition, the statistically significant higher SLEDAI score in atherosclerotic patients and higher frequency of moderate and severe disease activity with presence of statistically significant positive correlation between the carotid IMT and SLEDAI score. All these previous results support that higher disease activity is strongly associated with presence of atherosclerosis in SLE. That association was concluded also by **khairy et al.**<sup>17</sup> who stated that SLEDAI score was higher in patients with atherosclerosis. These results come in agreement with **Belibou et al.**<sup>21</sup> study who concluded that there was a positive correlation between IMT and SLEDAI score. However, **Manzi et al.**<sup>22</sup> found an inverse relationship between disease activity and carotid plaque. In addition, our results go hand in hand with the results of **Soliman et al.**<sup>23</sup> who concluded that 50% of patients with high SLEDAI score have increased IMT, while 25% of the patients who had moderate increase in SLEDAI score had increased IMT and the results were highly significant.

Based on the comparison between the two groups regarding nail fold capillary microscopic results, results of this study showed that the capillary length, width and arterial diameter were statistically significantly higher in atherosclerotic patients, while capillary density was statistically significantly lower in those patients. In addition, meandering, tortuous and disorganized capillaries were significantly more frequent among atherosclerotic cases. However, there was no statistically significant difference among the studied groups regarding the presence of corkscrew or bushy capillaries. On the other hand, results of **Ragab et al.**<sup>24</sup> reported that meandering, tortuous, corkscrew, bushy capillaries were found in atherosclerotic SLE patient by 45%, 16%, 15% and 7.5%, while capillary enlargement and hemorrhage were found to be 22.5% and 10%. In addition, results of this study are supported by **Yuksel et al.**<sup>25</sup> studied 25 SLE patients and demonstrated that the capillaroscopic abnormalities included dilatation & hemorrhage and

tortuosity that were 5.7 times more frequent among those patients with atherosclerosis.

Results of current study showed that the arterial limb diameter had highest diagnostic performance in diagnosing atherosclerosis with arterial diameter  $\geq 17.0$   $\mu\text{m}$ . This is nearly similar to **Ragab et al.**<sup>24</sup> who reported that meandering of capillaries and arterial limb diameter are of most important values to diagnose atherosclerosis in SLE.

On correlating IMT with various parameter of nail fold capillary microscopy, there was significant positive correlation with capillary length, capillary width and arterial limb diameter and inverse correlation with capillary density. However, we didn't find studies discussing this correlation yet.

## CONCLUSIONS

We concluded that atherosclerosis is common in SLE and it is associated with higher disease activity. In addition, nail fold capillary microscopy is helpful in the detection of atherosclerosis in SLE patients, the capillaroscopic findings may reflect the changes of the intima media thickness, and it may be correlated with these changes.

**Limitations of the study:** Small sample size is the main limitation of this study.

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