Carotid Media Thickness Measurement as a Marker of Premature Atherosclerosis in SLE Patients with and Without Nephritis

Fayza Ibrahim Fouad Lashin[1], Reda Abdel Samea Al Arabawy[2], Mohammed Hasan El Nagar[1], Amr Abdelaal Elsheikh[1]

[1]Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[2]Radiodiagnosis Department, Faculty of Medicine, Tanta University, Tanta, Egypt
aseal2016amr@yahoo.com

Abstract: This study was performed to evaluate carotid media thickness measurement as a marker of premature atherosclerosis in systemic lupus erythematosus (SLE) patients with and without nephritis. This study involved 30 patients with SLE without nephritis **(GI)** (females 26 (86.7%) and males 4 (13.3%)) with mean age of 28.60 ± 588 years and with mean disease duration of (4.95±3.61) years. Also involved 30 patients with SLE with nephritis **(GII)** (females 25 (83.3%) and males 5 (16.7%) with mean age of 29.67 ± 6.16 years and with mean disease duration of 7.20 ± 3.53 years in addition to 30 healthy volunteers **(GIII)** (21 females and 9 males with mean age (28.53 ± 5.35 years) as control group. Patients are diagnosed as SLE according to the American College of Rheumatology (ACR) criteria or Systemic lupus International Collaborating Clinics (SLICC) 2012 criteria. **All patients were subjected to the following:** Complete history taking, Full clinical examination, Laboratory investigation, Doppler examination of the extra-cranial portion of the carotid arteries to measure the intima-media thickness (IMT). **The results showed the following: (1)** There was significant difference between GI & GII (p1:0.048) regarding intima media thickness. (2) There was significant difference between GI & GIII (p2:0.005) regarding intima media thickness. (3) There was significant difference between GII & GIII (p3:0.001) regarding intima media thickness. (4) There was significant difference between GI & GII (P1:0.001) & GII & GIII (P3:0.001) regarding serum urea. (5) There was significant difference between GI & GII (P1:0.005) & GII & GIII (P3:0.006) regarding serum creatinine. (6) There was no significant difference between GI & GIII (P2:0.126) & (P2:0.962) regarding serum urea and creatinine respectively. (7) There was significant difference between GI & GII (P1:0.001) and between GII & GIII (P3:0.001) regarding both Albumin/Creatinine ratio and 24h protein. (8) There was no significant difference between GI & GIII (P2:0.540), (P2:0.763) regarding both Albumin/Creatinine ratio and 24h protein respectively. (9) There was significant difference between GI & GII (P1:0.032) and GI & GIII (P2:0.001) and GII & GIII (P3:0.001) regarding cholesterol. (10) There was significant difference between GI & GII (P1:0.001) and GI & GIII (P2:0.029) and GII & GIII (P3:0.001) regarding triglycerides. (11) There was significant difference between GI & GII (P1:0.001) and GI & GIII (P2:0.017) and GII & GIII (P3:0.001) regarding low density lipoproteins. (12) There was no significant difference between patient and control groups regarding fasting blood glucose and complete blood picture. (13) There was significant difference between GII and other studied groups (P: 0.001) regarding urinary albumin. Correlation between Intima media thickness (IMT) and clinical and laboratory data among GI showed positive correlation between cholesterol, triglycerides and IMT. Correlation between Intima media thickness (IMT) and clinical and laboratory data among GII showed positive correlation between age, cholesterol, triglycerides, LDL, serum urea, serum creatinine, 24h protein and Albumin/Creatinine ratio and IMT.

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1. Introduction

Systemic lupus erythematosus (SLE):

Is the prototype of systemic autoimmune disease (AD). Immune system activation in SLE is characterized by exaggerated B-lymphocyte and T-lymphocyte responses and loss of immune tolerance against self-antigens. Production and defective elimination of antibodies, circulation and tissue deposition of immune complexes, and complement and cytokine activation contribute to clinical manifestations that range from fatigue and joint pain to severe, life-threatening organ damage. (1)

Etiology:

The exact etiology of SLE remains unclear. A complicated and multifactorial interaction among various genetic and environmental factors is probably involved. (2)

Lupus nephritis:

Is histologically evident in most patients with systemic lupus erythematosus even those without

clinical manifestations of renal disease. Evaluating renal function in SLE patients is important because early detection and treatment of renal involvement can significantly improve renal outcome. [3]

Atherosclerosis:

was believed to be caused by passive deposition of lipids into arterial walls, with subsequent covering of the deposits by smooth muscle and endothelial cells; however, we now know that this disease results from dynamic accumulation of oxidized cholesterol over time, primarily driven by activity of the immune system. [4]

Pathologic intimal thickening to fibroatheroma are accompanied by early lipid accumulation, followed by macrophage infiltration with defective clearance of apoptotic bodies along with decrease in proteoglycan and hyaluronan in lipid pools that convert to necrotic cores. [5]

In SLE, despite a similar anatomic distribution of atherosclerosis to non-SLE patients, those with SLE may harbor more inflamed plaques considered more likely to cause thrombotic complications. Indeed, in experimental atherosclerosis, systemic or remote inflammation elicits an 'echo' of increased inflammation in arterial lesions. [4]

The pathophysiology of accelerated atherosclerosis in SLE is mediated by factors such as inflammatory processes in the vascular wall, specific antibodies, dyslipoproteinemia, endothelial dysfunction and the high prevalence of traditional risk factors for cardiovascular diseases. [6]

SLE patients with nephritis are at a higher risk to develop arterial stiffening, leading to early end-organ damage. Early aggressive treatment may prevent endothelial dysfunction. [7]

Increased intima media thickness (IMT) is a non-invasive marker of early arterial wall alteration, which is easily assessed in the carotid artery by B-mode ultrasound, and more and more widely used in clinical research. Methods of IMT measurement can be categorized by two approaches measurement at multiple extra cranial carotid sites in near and far walls. [8]

B-mode ultrasound allows detection and measurement of the intima media wall thickness (IMT) and degree of plaque in the carotid arteries. IMT may be the most sensitive marker for the earliest stages of atherosclerosis and is considered to be a marker of generalized atherosclerosis. [5]

Atherosclerosis occurred in 40% young aged female SLE patients as CIM thickening and/or carotid plaque. There was positive correlation of CIM thickness with age, duration of SLE disease. [9]

Aim of the Work

The aim of this study was to evaluate carotid media thickness measurement as a marker of premature atherosclerosis in SLE Patients with and without nephritis.

2. Patients and Methods

Patients:

90 patients that were recruited in outpatient Rheumatology and Clinical Immunology clinic at department of Internal Medicine Tanta University

Group (I): 30 SLE patients without nephritis, **Group (II):**30 SLE patients with nephritis, **Group (III):** 30 healthy subjects as a control group.

The Study Design:

- This is a cross sectional study.

Study approval

A – Ethics

Permission was obtained from Research Ethics Committee as a part of Quality Assurance Unit in Faculty of Medicine at Tanta University to conduct this study and to use the facilities in the hospital.

B – Consent

Informed written consent was obtained from all patients after full explanation of benefits and risks of the study. Privacy of all patients' data was granted by a special code number for every patient file that includes all investigations.

Possible Hazards during the research

- Liability to infection for patients or doctor or both, this can be avoided by sampling at complete aseptic precautions, according to the parameters of infection control.
- No other hazards expected during the period of research.
- There will be safe disposal of waste products e.g., needles…etc.
- Any unexpected risks appear during the course of the research will be cleared to participants and the ethical committee on time.

Inclusion criteria:

Patients fulfilling American College of Rheumatology [11] or Systemic lupus International Collaborating Clinics (SLICC) 2012 criteria [10] for diagnosis of systemic lupus erythematosus with disease duration more than two years for lupus erythematosus and more than six months for lupus nephritis.

Exclusion criteria:

- Patients with history of cardiovascular diseases.
- Patients with history of neck trauma.
- Patients with history of neck irradiation.
- Patient with carotid artery atherosclerosis. (by HTN & DM)
- Patient with diabetes and hypertension.

Control: Control subjects were 30 healthy volunteers selected from the same geographical area, matched to patient age and sex.

All control subjects were on the same exclusion criteria.

Data collection:

All patients and controls were subjected to:

1. Thorough history taking:

Regarding: age, sex and duration of the disease.

2. Complete clinical examination:

Particularly for presence of; butterfly rash, discoid rash, photosensitivity, oral ulcers, hair loss, peripheral edema, arthritis, serositis, fever, CNS affection and hypertension.

3. Laboratory Investigations

Urine analysis., Protein in 24 hour urine collection, Urinary albumin/creatinine ratio, ANA, Anti-ds. DNA, CBC, Random & fasting blood glucose, Lipid profile. (LDH, HDL, TG, Cholesterol). On the basis of the mean values, hypercholesterolemia and hypertrigly ceridaemia were defined as a total serum **cholesterol** (2001) mg/dl, or a serum **triglyceride** (200) mg/dl, Complement level (C3 & C4), Serum urea and serum creatinine.

4. Sonographic evaluation of intima media thickness

- The patients and controls were scanned using Helwett Packard SONOS 2000 with 7.5 MHz transducer.
- Intima media thickness (IMT) is measured:
  - Two centimeters proximal to the bifurcation of the common carotid artery.
  - Common carotid artery (1cm before the bulb).
  - Bulb.5-1cm cranially to the start of the bulb.
  - Internal carotid artery 1 cm after flow divider.
- For each patient the highest IMT among the four segments bilaterally studied were used.
- According to current sonographic criteria we refer to normal "IMT" when complex IMT is ≤ 0.9mm, IMT > 0.9mm were considered indicative of thickened intima and IMT value > 1.3mm indicative of atherosclerotic plaque.
- All exams carried out by a single specialist physician, and all images were taken.

Patient position: The patient lie down in the supine or semi-supine position with head tilted away from side being examined.

Carotid Artery versus Jugular Vein: The common carotid artery (CCA) lies immediately adjacent to the jugular vein, but the two vessels are easily differentiated. First, flow- in the carotid artery is toward the head and pulsatile. In contrast, flow in the jugular vein is toward the feet and has typical venous flow- features. (Low Velocity, undulating flow pattern.

Caliber of the carotid artery is fairly uniform, whereas the caliber of the jugular vein varies markedly from moment to moment, in response to respiration. Finally, the carotid arteries are thick walled, and a distinct intimal reflection is visible. The jugular vein wall is thin and the vein collapses with slight pressure from the transducer.

Carotid artery	Jugular vein
Located medially	Laterally
Pulsatile on compression	Collapse on compression
Rounded uniform caliper	Oval & vary with respiration
High velocity	Low velocity, undulating flow
Thick wall	Thin wall (invisible)

5. Statistical analysis

- Data were collected, tabulated and statistically analyzed.
- All values were expressed as mean ± SD.
- Means between groups were compared using ANOVA or independent sample t-test (depending on the number of groups) with Tukey's post-hoc test.
- Correlation was measured using Pearson's test. SPSS v.19.0 was used; $p < 0.05$ was considered significant.
- Chi-square test (χ^2): was used to study association between two qualitative variables.

3. Results

This study involved: 90 subjects were recruited from outpatient Rheumatology and Clinical Immunology clinic at department of Internal Medicine Tanta University.

- **Group I:** 30 patients with SLE without nephritis. **(GI)**
- **Group II:** 30 patients with SLE with nephritis. **(GII)**
- **Group III:** 30 healthy subjects. **(GIII)**

Statistical analysis:

All values were expressed as mean ± SD.

Means between groups were compared using ANOVA or independent sample t-test (depending on the number of groups) with Tukey's post-hoc test.

Correlation was measured using Pearson's test.

SPSS v.19.0 was used; $p<0.05$ was considered significant.

Table (1): Demographic data of studied groups:

		Group I	Group II	Group III	Test	p. value
Age	Range	18 – 37	18 – 38	19 – 36	F: 0.360	0.699
	Mean ± S. D	28.60 ± 5.88	29.67 ± 6.16	28.53 ± 5.35		
Sex	Male (%)	4 (13.3%)	5 (16.7%)	9 (30%)	X^2: 2.917	0.233
	Female (%)	26 (86.7%)	25 (83.3%)	21 (70%)		

χ^2: Chi square test S. D: Stander deviation
F: for ANOVA test, Pairwise comparison between each 2 groups was done using Post Hoc Test (Tukey)
P: p value for comparing between the different groups
- Group I: 30 SLE patients without nephritis. (GI)
- Group II: 30 SLE patients with nephritis. (GII)
- Group III: 30 healthy subjects. (GIII)

This table shows no significant difference between patients and control regarding age and gender.

Table (2): Serum urea and serum creatinine among studied groups:

		Range	Mean ± S. D	F. test	p. value		
Urea (mg/dl)	**Group I**	19 – 50	28.65 ± 8.27	12.402	0.001*	P1	0.001*
	Group II	19 – 80	39.27 ± 18.64			P2	0.126
	Group III	14 – 36	23.73 ± 6.43			P3	0.001*
Creatinine (mg/dl)	**Group I**	0.58 – 1.6	0.90 ± 0.22	5.346	0.006*	P1	0.005*
	Group II	0.6 – 3.0	1.25 ± 0.77			P2	0.962
	Group III	0.6 – 1.21	0.91 ± 0.18			P3	0.006*

χ^2: Chi square test S. D: Stander deviation
F: F for ANOVA test, Pairwise comparison between each 2 groups was done using Post Hoc Test (Tukey)
P: p value for comparing between the different groups
- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
- *: Statistically significant at $p \leq 0.05$
- Group I: 30 patients with SLE without nephritis. (GI)
- Group II: 30 patients with SLE with nephritis. (GII)
- Group III: 30 healthy subjects. (GIII)

Table shows significant difference between GI & GII and GII & GIII and no significant difference between GI & GIII regarding serum urea and serum creatinine.

Table (3): Albumin/Creatinine ratio and 24 hour urinary protein collection among studied groups:

		Range	Mean ± S. D	F. test	p. value		
Albumin / creatinine ratio	**Group I**	3.15 – 29.4	14.91 ± 7.26	10.164	0.001*	P1	0.001*
	Group II	3.08 – 630	97.13 ± 154.71			P2	0.540
	Group III	0.1 – 1.2	0.72 ± 0.26			P3	0.001*
24 hrs. protein	**Group I**	45 – 420	215.81 ± 100.04	10.720	0.001*	P1	0.001*
	Group II	98 – 9000	1488.98 ± 2216.11			P2	0.763
	Group III	110 – 123	115.70 ± 3.46			P3	0.001*

S. D: Stander deviation
F: F for ANOVA test, Pairwise comparison between each 2 groups was done using Post Hoc Test (Tukey).
P: p value for comparing between the different groups
- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
- *: Statistically significant at $p \leq 0.05$
- Group I: 30 patients with SLE without nephritis. (GI)
- Group II: 30 patients with SLE with nephritis. (GII)
- Group III: 30 healthy subjects. (GIII)

Table shows significant difference between GI & GII and GII & GIII but no significant difference between GI & GIII regarding Albumin/Creatinine ratio and 24 hour urinary protein collection.

Table (4): Lipid profile between studied groups:

		Range			Mean	±	S. D	F. test	p. value		
Cholesterol (mg/dl)	**Group I**	104	–	230	187.10	±	33.41	15.580	0.001*	P1	0.032*
	Group II	120	–	303	208.34	±	54.77			P2	0.001*
	Group III	133	–	182	154.37	±	12.44			P3	0.001*
TG (mg/dl)	**Group I**	42.6	–	306	161.02	±	82.68	17.252	0.001*	P1	0.001*
	Group II	83	–	779	288.00	±	221.60			P2	0.029*
	Group III	70	–	99	82.63	±	9.38			P3	0.001*
LDL (mg/dl)	**Group I**	48	–	205	111.43	±	47.06	26.225	0.001*	P1	0.001*
	Group II	60	–	210	154.60	±	41.94			P2	0.017*
	Group III	45	–	135	83.70	±	20.18			P3	0.001*
HDL (mg/dl)	**Group I**	30	–	77	55.97	±	12.23	1.590	0.210	P1	0.101
	Group II	32	–	77	51.53	±	11.30			P2	0.169
	Group III	40	–	67	52.27	±	6.52			P3	0.784

S. D: Stander deviation. LDL: Low density lipoprotein.
HDL: High density lipoprotein. TG: Triglycerides.
F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
P: p value for comparing between the different groups

- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
- *: Statistically significant at $p \leq 0.05$
  - Group I: 30 patients with SLE without nephritis. (GI)
  - Group II: 30 patients with SLE with nephritis. (GII)
  - Group III: 30 healthy subjects. (GIII)

Table shows significant difference between GI & GII and GI & GIII and GII & GIII regarding cholesterol, triglycerides and low density lipoprotein but shows no significant difference between GI & GII and GI & GIII and GI & GIII regarding high density lipoprotein.

Table (5): Fasting blood sugar among studied groups:

		Range			Mean	±	S. D	F. test	p. value		
FBS	**Group I**	56	–	110	84.77	±	10.59	1.784	0.174	P1	0.700
	Group II	75	–	120	85.70	±	10.24			P2	0.163
	Group III	71	–	95	81.37	±	6.74			P3	0.076

S. D: Stander deviation. FBS: Fasting blood sugar.
F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey).
P: p value for comparing between the different groups

- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
  - Group I: 30 patients with SLE without nephritis. (GI)
  - Group II: 30 patients with SLE with nephritis. (GII)
  - Group III: 30 healthy subjects. (GIII)

Table (6): Complete blood count between studied groups:

		Range			Mean	±	S. D	F. test	p. value		
Hb (g/dl)	**Group I**	10	–	14.8	11.94	±	1.39	2.310	0.105	P1	0.174
	Group II	10.1	–	14	12.38	±	1.12			P2	0.057
	Group III	11	–	14	12.61	±	1.15			P3	0.456
Platelets (mm^3)	**Group I**	80	–	450	246.47	±	79.50	0.401	0.671	P1	0.434
	Group II	64	–	402	230.33	±	82.91			P2	0.985
	Group III	159	–	417	246.07	±	76.07			P3	0.446
WBCs (mm^3)	**Group I**	2.2	–	13.1	6.56	±	3.10	1.641	0.200	P1	0.610
	Group II	2	–	14.8	6.91	±	3.06			P2	0.082
	Group III	6	–	11	7.76	±	1.29			P3	0.215

S. D: Stander deviation. Hb: Heamoglobin. WBCs: white blood cells. F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey) P: p value for comparing between the different groups

- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
  - Group I: 30 patients with SLE without nephritis. (GI)
  - Group II: 30 patients with SLE with nephritis. (GII)
  - Group III: 30 healthy subjects. (GIII)

Table (7): Urine analysis among studied groups:

	Group I		Group II		Group III		X^2	P-value
	N	%	N	%	N	%		
Hematuria (RBCs > 5 cells/HPF)	5	16.7	10	33.3	4	13.3	4.142	0.126
Pyuria (Pus cells > 5 cells/HPF)	4	13.3	5	16.7	2	6.7	1.452	0.484
Albumin	2	6.7	15	50	1	3.3	25.423	0.001*

χ^2: Chi square test S. D: Stander deviation
F: for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post
p: p value for comparing between the different groups.
*: Statistically significant at $p \leq 0.05$.

- Group I: 30 SLE patients without nephritis. (GI)
- Group II: 30 SLE patients with nephritis. (GII)
- Group III: 30 healthy subjects. (GIII)

This table shows that 13.3% of patients at GI and 16.7% at GII and 6.7% at GIII had pyuria, 30% of patients had albumin in urine and 16.7% of patients at GI and 33.3% at GII and 13.3% at GIII had hematuria. Albumin present at 6.7% at GI and 50% at GII and 3.3% at GIII.

Table (8): Complement (C3 & C4) among studied groups:

		Range	Mean ± S. D	F. test	p. value		
C 3 (mg/dl)	**Group I**	60 – 157.4	114.66 ± 25.37	11.407	0.001*	P1	0.003*
	Group II	35 – 157	89.08 ± 23.17			P2	0.248
	Group III	85 – 175	123.33 ± 27.54			P3	0.001*
C 4 (mg/dl)	**Group I**	8 – 50	28.14 ± 12.21	14.838	0.001*	P1	0.001*
	Group II	5 – 45	16.55 ± 9.43			P2	0.267
	Group III	12 – 51	31.33 ± 11.36			P3	0.001*

S. D: Stander deviation C 3: complement 3 C 4: complement 4
F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
P: p value for comparing between the different groups

- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
- *: Statistically significant at $p \leq 0.05$
- Group I: 30 patients with SLE without nephritis. (GI)
- Group II: 30 patients with SLE with nephritis. (GII)
- Group III: 30 healthy subjects. (GIII)

Table (8): shows significant difference between GI & GII and GII & GIII regarding serum complement (C3) and serum complement (C4). But no significant difference between GI & GIII.

Table (9): Immune profile among studied groups:

			Group I	Group II	Group III	X^2	P-value
ANA	**+ve**	**N**	28	29	3	**65.102**	**0.001***
		%	93.3%	96.7%	10.0%		
	-ve	**N**	2	1	27		
		%	6.7%	3.3%	90.0%		
Anti- ds DNA	**+ve**	**N**	27	28	0	**70.782**	**0.001***
		%	90.0%	93.3%	0%		
	-ve	**N**	3	2	30		
		%	10.0%	6.7%	100.0%		

χ^2: Chi square test . D: Stander deviation p: p value for comparing between the different groups.

- Group I: 30 SLE patients without nephritis. (GI)
- Group II: 30 SLE patients with nephritis. (GII)

Table (10): Results of renal biopsy at GII:

Biopsy	N	%
II	2	**6.7**
III	12	**40.0**
IV	10	**33.3**
V	6	**20.0**
Total	**30**	**100.0**

Table (11): Ultrasound (U/S) findings among study group:

	Group I		Group II		Group III	
	N	%	N	%	N	%
Negative US findings (<0.9mm)	21	70	15	50	25	83.3
Increased IMT only (>0.9 to <1.3 mm)	5	16.7	7	23.3	3	10
Increased IMT with plaque (>1.3mm)	4	13.3	8	26.7	2	6.7

IMT: intima media thickness. US: Ultra sound.

- Group I: 30 patients with SLE without nephritis. (GI)
- Group II: 30 patients with SLE with nephritis. (GII)
- Group III: 30 healthy subjects. (GIII)

This table shows that 70% of subjects at GI and 50% at GII and 83.3% at GIII have negative ultrasound findings and 16.7% of subjects at GI and 23.3% at GII and 10% at GIII have positive ultrasound findings shows increased IMT only and 13.3% of subjects at GI and 26.7% at GII and 6.7 % at GIII have positive ultrasound findings shows increased IMT with plaque.

Table (12): Intima media thickness measurement among study groups:

		Range			Mean	±	S. D	F. test	p. value		
CIMT	**Group I**	0.4	–	1.6	0.79	±	0.37	11.983	0.001*	P1	0.048*
	Group II	0.4	–	1.6	0.99	±	0.42			P2	0.005*
	Group III	0.2	–	1.3	0.52	±	0.32			P3	0.001*

S. D: Stander deviation F: F for ANOVA test, Pairwise comparison between each 2 groups was done using Post Hoc Test (Tukey)

P: p value for comparing between the different groups

- p_1: p value for comparing between group I and group II
- p_2: p value for comparing between group I and group III
- p_3: p value for comparing between group II and group III
- *: Statistically significant at $p \leq 0.05$
- Group I: 30 patients with SLE without nephritis. (GI)
- Group II: 30 patients with SLE with nephritis. (GII)
- Group III: 30 healthy volunteers. (GIII)

Table shows significance between GI & GIII, GII & GIII, GI & GII regarding CIMT.

Table (13): Relation between clinical data and ultrasound (U/S) findings at group

Group I	CIMT	
	r.	P
Age	0.241	**0.321**
24 hrs. protein	0.117	**0.537**
Albumin / Cr Ratio	0.162	**0.394**
TG	0.623	**0.001***
Cholesterol	0.419	**0.021***
LDL	0.612	0.001*

Table shows positive correlation between IMT and (triglycerides, cholesterol and low density lipoprotein) respectively at **GI**.

Table (14): Relation between clinical data and ultrasound (U/S) findings at group II:

Group II	CIMT	
	r.	P
Age	0.759	**0.001***
24 hrs protein	0.571	**0.001***
Albumin / creatinine ratio	0.552	**0.002***
Urea	0.765	**0.001***
Creatinine	0.683	**0.001***
TG	0.514	**0.004***
Cholesterol (Cho)	0.481	**0.007***
LDL	0.793	**0.001***

Table showing positive correlation between IMT and (Age, 24 hrs. protein, Albumin / creatinine ratio, urea, creatinine, triglycerides, cholesterol, and low density lipoprotein) respectively at **GII**.

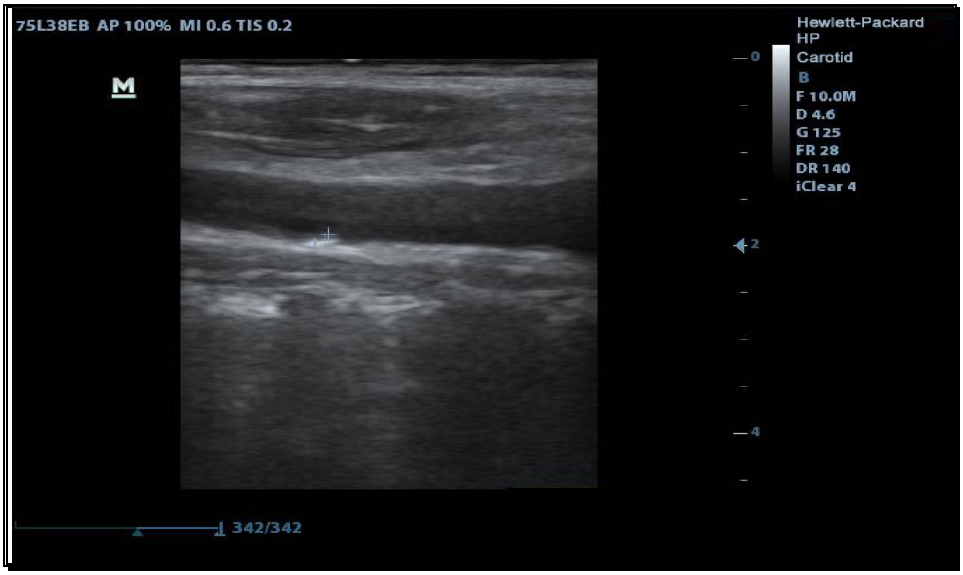

Figure (1): Longitudinal grey scale image showing normal CIMT

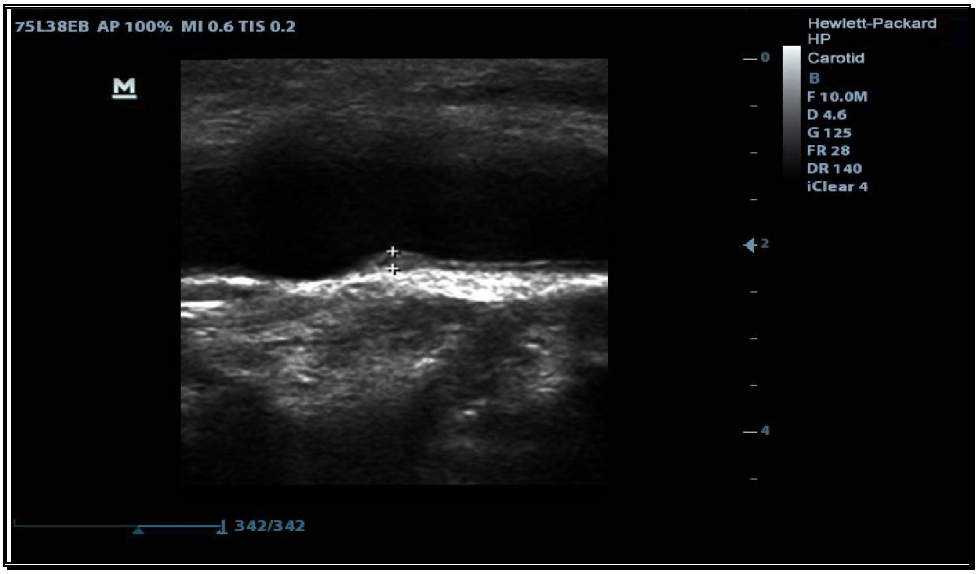

Figure (2): Longitudinal grey scale image showing small non-calcified atheromatous plaque at the carotid bulb. It measures 3.2x1.2mm.

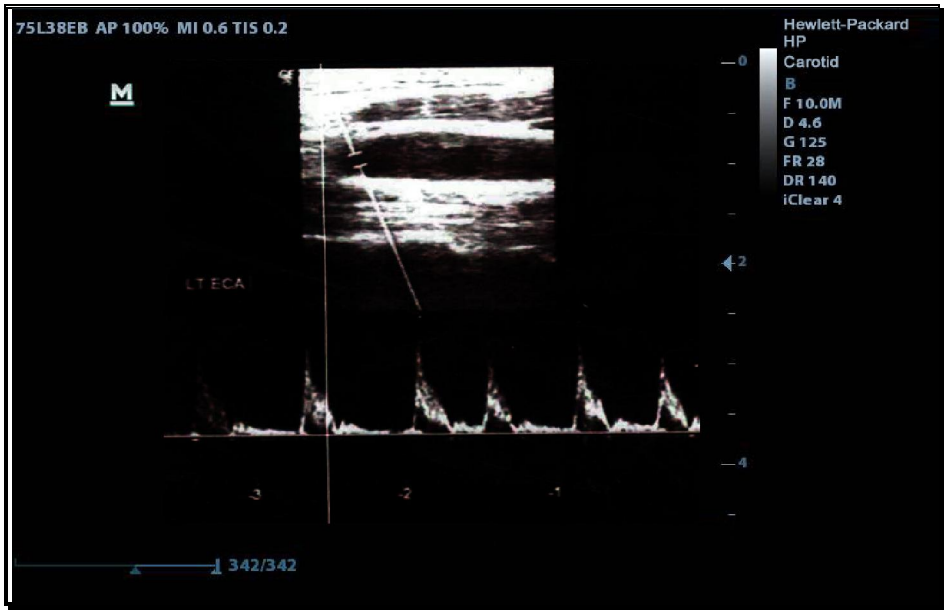

Figure (3): Longitudinal grey scale image showing increase CIMT measures 1.3mm.

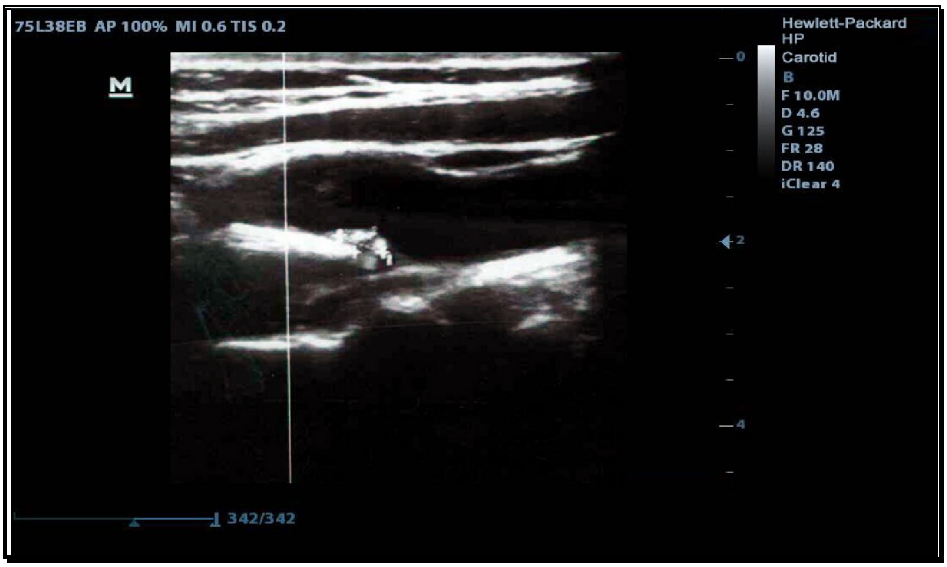

Figure (4): Longitudinal grey scale image showing small non-calcified atheromatous plaque. It measures 2.5x1.6mm.

4. Discussion

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organ systems and characterized by a fluctuating disease course. The disease activity can range from mild to severe, and the consequences might be significant morbidity and organ damage and increased mortality. [12]

Lupus Nephritis, which is mediated by immune complex depositions in the glomeruli and inflammatory tubulointerstitial changes. LN affects 16 -45% of patients with SLE, 10-20% of whom will develop end-stage renal disease over time. [13]

Atherosclerosis is an inflammatory disease and has been widely accepted as one of the strongest predictors of major CV events. [14]

The carotid intima-media thickness (CIMT) is a widely used surrogate marker for atherosclerosis worldwide. The carotid IMT can be simply, noninvasively, and reproducibly measured through B-mode carotid ultrasound. The carotid IMT is also a strong predictor of future cerebral and cardiovascular events. [15]

Carotid intima–media thickness (CIMT), assessed by B or M mode ultrasound at the carotid artery level, is one of the non-invasive measures to

evaluate and follow subclinical atherosclerosis, as recommended by the American heart association. [16]

Premature atherosclerosis in systemic lupus erythematosus (SLE) was first noted in necropsy studies reported by Bulkley and Roberts in 1975 and subsequently confirmed in a survival study by Urowitz et al in 1976. Since then early clinical 3–6 and subclinical 7–10 atherosclerotic features have been demonstrated in SLE by several groups.

Because premature atherosclerosis cannot be explained by the Framingham risk factors alone, it has been attributed to complex interactions between traditional risk factors and factors associated with the disease itself or its treatment. [17]

Despite recent achievements in defining risk factors for subclinical atherosclerosis and for the progress of preclinical atherosclerosis associated with SLE, the role of individual traditional and non-traditional risk factor in SLE is still controversial. [16]

Atherosclerosis occurs prematurely in patients with systemic lupus erythematosus and is independent of traditional risk factors for cardiovascular disease. The clinical profile of patients with lupus and atherosclerosis suggests a role for disease-related factors in atherogenesis. [18]

The aim of our study was to evaluate the carotid artery intima-media thickness (IMT) as a marker of premature atherosclerosis in SLE patient with and without nephritis.

Our study included 30 patients with SLE without nephritis **(GI)** with mean age of 28.60 ± 5.88 & 30 patients with lupus nephritis **(GII)** with mean age of 29.67 ± 6.16 and 30 healthy subjects **(GIII)** with mean age of 28.53 ± 5.35.

The selection of patients was based on the modified American college of rheumatology (ACR) criteria for classification of SLE [19] and The 2012 systemic lupus international collaborating clinics (SLICC) criteria. [20]

The results of this study shows that five of **(GI)** SLE patients (16.7%) showed positive (+ve) sonographic findings (significant increase in IMT thickness i.e. IMT > 0.9 mm & < 1.3 mm without plaque). four of them (13.3%) showed increased of intima media thickness > 1.3 mm with plaque. Seven (70%) of SLE patients showed negative (-ve) sonographic findings (IMT<.9mm). **(Table 11)**

Regarding **(GII)** seven 23.3% of patients with LN in our study showed positive (+ve) sonographic findings (significant increase in IMT thickness i.e. IMT > 0.9 mm & < 1.3 mm without plaque). Eight of them (26.7%) showed increased of intima media thickness > 1.3mm with plaque. fifteen (50%) of lupus nephritis patients showed negative (- ve) sonographic findings (IMT< 0.9mm). **(Table 11)**

Regarding **(GIII)** two 6.7% of healthy subjects in our study showed positive (+ve) sonographic findings i.e. (significant increase in IMT thickness i.e. IMT >1.3 mm with plaque). Three of them (10 %) showed increased of intima media thickness > 0.9 mm & < 1.3 mm without plaque. Twenty five subjects (83.3%) of **GIII** showed negative (- ve) sonographic findings (IMT < 0.9 mm). **(Table 11)**

The study showed significant difference between patients with SLE without nephritis **(GI)** & healthy subjects **(GIII)** (P2: 0.005). **(Table 12)**

regarding **CIMT** which is in cope with **(Fadda S et al., 2014)** [21] which gave results of radiological evaluation by ultrasonography revealed positive findings in 15 (30%) of patients (i.e. IMT > 0.9 mm). Out of these 15 patients, 3 (6%) showed plaque formation. The results of this study showed very highly significant statistical differences in IMT between SLE patients and controls. Also our results are in coordinate with **(Henrot, P et al., 2018)** [22]who shows that, compared to healthy controls, SLE patients had a significantly increased CIMT (mean difference of 0.08 mm, 95% CI (0.06-0.09), P<0.05).

Also **(Smrzova et al, 2014)** [23]study which included 63 patients with SLE (female: male 53:10, mean age 38.4±12.7 years, the control group consisted of 24 volunteers (female: male 20:4 mean age 31.04±8.59). Intima media thickness (IMT) was measured by ultrasound on both sides. Their results showed a significant difference of IMT (P ≤ 0.03) between the lupus patients and sex-age adjusted healthy controls with mean IMT in SLE patients of 0.569 ± 0.11 mm, in control group 0.495±0.05 mm which copes with our results.

Regarding **(GII)** SLE with nephritis **CIMT** measurements i.e. (Increased IMT with plaque (> 1.3mm) include 26.7 % (8) of LN patients.

(Increased IMT only (> 0.9 to <1.3 mm) include (7) 23.3% of LN patients and negative US findings (< 0.9 mm**)** include (15) 50% of **(GII)** LN patients.

Our study shows **CIMT** significantly increased between **(GII)** & **(GIII)** healthy subjects group. (P3: 0.001) **(Table: 12).**

So our results are in accordance with **(Sazliyana, S et al 2011)** [24] which gave results of fourteen patients (16.9%) had thickened CIMT and three (3.6%) had carotid plaques. The mean CIMT for this LN cohort was 0.6 - 0.2 mm. Compared with age and sex-matched controls from the carotid atherosclerosis progression Study (CAPS) and using the 75th percentile as the cut off, 14 (16.9%) LN patients had thickened CIMT. Only three (3.6%) patients had carotid plaques.

Also**, (McHugh J, 2017)** [25] showed results in cope with our study with results of clinical subgroup

analysis of patients with systemic lupus erythematosus (SLE) (n = 281) and age and sex-matched population controls reveals that accelerated atherosclerosis is mainly confined to a subgroup of patients with SLE and nephritis.

The patients with nephritis had significantly more carotid plaques than their respective controls (P = 0.008), which was not the case for the patients with anti-phospholipid antibodies.

Plaques occurred twice as often in the patients with nephritis (23%) than in the patients without nephritis (11%, P = 0.038) or in controls (12%, P = 0.035).

In our study we found significant difference regarding **CIMT** between patients with nephritis **(GII)** & patients without nephritis **(GI)** (P1:0.048) **(Table: 12)** correlated with **(Zhang, M et al, 2014)** [(26)] which reported that prevalence of carotid artery plaques were detected in 46 patients with LN (21.90%), 24 patients with SLE (16.00%) and 13 healthy controls (6.50%). The prevalence of carotid artery plaque was significantly higher in patients with LN (GII) compared with that in patients with SLE without nephritis (P, 0.05) and healthy controls (P, 0.01).

Also our results are in cope with **(Hermansen, M. L, et al (2018)** [(27)] that showed 147 SLE patients, 74 had LN. Median age of the study cohort was 46 years, 89% were women and median eGFR was 89 ml/min/1.73 m^2. Carotid artery calcification (CAC) score > 0 was present in 57 (39%) and carotid plaque in 29 (20 %) of the SLE patients. The presence of CAC and/or carotid plaque was highest in SLE patients with impaired renal function. Regression analysis showed that comparison between SLE patients without LN and eGFR equal or more 70 ml/min/1.73 m^2 (reference group), and those had LN and impaired renal function was associated with the presence of CAC. And also cope with**, (McHugh J, 2017)** [(25)]

On other hand our study is not correlated with **(Sharma, S. K. et al, 2016)** [(28)] which concluded that CIMT values did not significantly differ in patients with LN compared to SLE without nephritis.

Regarding urinary albumin Statistical data shows significant difference (P. value: 0.001) **(table:14)**, between lupus nephritis (GII) and other studied groups in cope with **(Donadio Jr et al, 1995)** [(29)]

We found significant difference in patients with nephritis **(GII)** & healthy subjects **(GIII)** (P3:0.001) **(table:3),** regarding albumin/creatinine ratio & 24h urinary protein which are in coordination with **(Christopher-Stine, L, et al 2004)** [(30)] and **(Leung, Y et al 2006)** [(31)]

Also significant difference found regarding albumin/creatinine ratio and 24h protein respectively between SLE patients without nephritis **(GI) &** patients with nephritis **(GII)** (P1:0.001) **(table:10)** in cope with **(Staveri, C 2016)** [(32)] **and (Medina‐Rosas, J et al 2016)** [(33)]

Regarding serum complement (**C4**) **(Table:8),** we found significant difference between patients without nephritis **(GI)** & patients with nephritis **(GII)**. P1:0.001 and between patients with nephritis **(GII)** & healthy subjects **(GIII)** p3:0.001in accordance with **(Sazliyana, S et al 2011)** [(24)]

In contrast to us **(Smrzova et al, 2014)** [(23)] study showed no significant difference.

Regarding complement (**C3**) **(Table:8),** our result but our results show significant difference between **(GI)** & **(GII)** and **(GII)** & **(GIII)** which copes with **Lewis, M. J et al (2012)** [(34)]

Our study revealed significant difference regarding (**C3**) **(Table:8),** between patients without nephritis **(GI)** & patients with nephritis **(GII)**. P1:0.003 and between patients with nephritis **(GII)** & healthy subjects **(GIII)** P3:0.001 in contrast with **(Sazliyana, S et al (2011)** [(24)] and **(Smrzova et al, 2014)** [(23)].

Significant difference regarding cholesterol and triglycerides (**table:4)** comparing patients without nephritis **(GI)** & healthy subjects **(GIII)** (P2:0.001 & 0.029) respectively in correlation with **(Ahmad Y., et al., 2007)** [(35)] who found significant statistic differences as regard serum cholesterol, triglyceride, between SLE patients with high IMT on sonographic evaluation and those with normal IMT and they concluded that triglycerides, age and the SLE itself are considered major risk factors contributing to the development of atherosclerosis in SLE patients. which, also our results are in cope with **(Asanuma, Y et al, 2003)** [(36)] regarding **(TG)** only who revealed that levels of total, high density lipoprotein, and low density lipoprotein cholesterol and LP (a) lipoprotein were similar in the two groups, but levels of triglycerides (P=0.02) and homocysteine (P <0.001) were significantly higher among the patients.

On other hand our results do not match with **(El-Magadmi, et el, 2004)** [(37)] regarding cholesterol but our results are in cope with **(El-Magadmi, et el, 2004)** [(37)] regarding triglycerides.

Therefore altered lipid profile is well documented in SLE patients and the association between dyslipoproteinemia and active SLE was described in several studies **(Ilowite et al., 1988)** [(38)], **(Borba and Bonfa 1997).** [(39)]

Statistically significant difference has found regarding (cholesterol & triglycerides) (**table:11),** when comparing patients with nephritis **(GII)** & healthy subjects **(GIII)** (P3:0.001) also our results

are cope with (**Austin, H. A et al 1999**) [40] and (**Zhang, M et al, 2014**) [26] butin contrast with (**Sazliyana, S et al 2011**) [44]

Comparison between patients without nephritis **(GI) &** patients with nephritis **(GII)** significant difference has found (P1:0.032) & (P1:0.0.001) regarding cholesterol and triglycerides respectively (**table:11),** which cope with **(Zhang, M et al, 2014)** [26]. Plaques were detected in 46 patients with LN (21.90%), 24 patients with SLE (16.00%) and 13 healthy controls (6.50%). The prevalence of carotid artery plaque was significantly higher in patients with LN compared with that in patients with SLE (P: 0.05) and healthy controls (P, 0.01).

Also results are in cope with **(Clark, W. F et al 1998)** [41] and **(Sharma, S. K. et al, 2016)** [28] regarding cholesterol.

Regarding low density lipoprotein **(LDL)** (**table:4),** we found significant difference between patients without nephritis (**GI) &** healthy subjects **(GIII)** (P2:0.017) in accordance with **(Roman M J et al 2003)** [42] reported that patients with lupus were older, higher systolic blood pressures and total and low density lipoprotein. (P: 0.01). also copes with (**McMahon M, et al, 2009**) [43], On other hand our results do not match with **(El-Magadmi, et el, 2004)** [36]regarding **LDL**.

Comparing patients without nephritis **(GI) &** patients with nephritis **(GII)** regarding **LDL** (**table:4),** our results show significant difference (P1: 0.001) in cope with (**Falaschi F, et al, 2000**) [44] who reported patients with NR proteinuria also had significantly levels of TC (*P* 5: 0.03), LDL cholesterol (*P* 5: 0.04) also in cope with **(Clark, W. F et al 1998)** [41]. but in contrast with **(Sharma, S. K. et al, 2016)** [28] who reveled (p:0.49) regarding **LDL.**

Comparing patients with nephritis (**GII) &** healthy subjects **(GIII)** regarding **LDL** significant difference (P3:0.001) (**table:11),** found in cope with (**Haddiya I, 2018**) [45] shows that mean age of patients was 34.63±12,7 years old, 83% were females. Class III, IV and V lupus nephritis accounted for 21%, 58.7% and 11.2% The prevalence of dyslipidemia with elevations in total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG) were noted in in LN patients.

We found significant difference regarding urea & creatinine (P1:0.001 & P1:0.005) (**table:2),** respectively comparing patients without nephritis **(GI)** & patients with nephritis **(GII).**

Also significant difference regarding urea & creatinine (P3:0.001 & P3:0.006) respectively (**table:2),** comparing patients with nephritis **(GII)** & healthy subjects **(GIII)** has been found in accordance with **(Najafi CC et al 2001)** [46] and **(Markowitz GS 2007)** [47] but in contrast with **(Sazliyana, S et al 2011)** [24]

Our results reveals positive correlation between **CIMT** of patient without nephritis (**GI**) and **(cholesterol, triglycerides and LDL) (table:13)** which are in cope with **(Smrzovaa et al, 2014)** [23] and no correlation regarding (age, 24 hrs. proteinuria, albumin / creatinine ratio) in contrast with **(Smrzovaa et al, 2014)** [23], **(Belibou et al, 2012)** [48] and (**McMahon et al, 2011).** [49]

Regarding patients with nephritis **(GII)** shows positive correlation with (**age, 24h protein, albumin/creatinine ratio, cholesterol, triglycerides, urea and creatinine) (table:14),** which copes with **(Sharma, S. K. et al, 2016)** [28] and **(Zhang, M et al, 2014)** [26].

Regarding patients with nephritis **(GII)** shows positive correlation between **CIMT** and **LDL** in accordance with **(Zhang, M et al, 2014)** [26] & in contrast with **(Sazliyana, S et al (2011)** [24]

Finally we can say that SLE itself is considered as a risk factor for accelerated atherosclerosis and this is amplified by multiple factors e.g. age of patients, duration of disease etc… and that the higher the number of risk factors in one patients the higher the incidence of premature atherosclerosis.

We can conclude that **CIMT** is reliable non-invasive marker for detection of premature atherosclerosis in SLE patients with and without nephritis. But also further and more studies still needed.

Also we can say that the differences between different studies in the evaluation of risk factors that leads to premature atherosclerosis may be attributed to many factors e.g.:

- Difference in methodology for assessment of atherosclerosis (Difference in Ultra sound equipment, difference in site and method of carotid measurement).
- Difference in selection of cases (regarding age, disease duration, therapy).
- Difference in cutoff point between normal and high IMT which differ between studies. In (**Marasini et al 2005**) [50] normal IMT was defined when IMT is ≤ 0.7mm while in (**Doria et al 2003**) [17] normal IMT is considered ≤ 0.9 mm.
- Difference in number of subjects and exclusion criteria.

limitations of our study

- Relatively short duration of study.
- Relatively small numbers of subjects in study.
- We did not take drugs taking by patients in consideration.
- Disease activity was not considered in our study.

- We did not exclude patients with obesity from study.
- There is no validated **CIMT** value for local or regional populations, therefore a comparison with a western-based population study may give rise to a lot of bias due to the multifactorial disparity between our and other populations.

5. Conclusion:

From this work we can conclude that:

- Systemic Lupus Erythematosus (SLE) is associated with increased risk of premature atherosclerosis and cardiovascular disease.
- SLE with nephritis is strongly associated with atherosclerosis.
- Doppler examination of the extra-cranial portion of the carotid arteries provides a useful non-invasive technique to measure the intima-media thickness (IMT) is dependable for detection of premature atherosclerosis in both SLE patients with and without nephritis.

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