Original Article

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Carotid Intima Media Thickness as a Marker of Atherosclerotic Burden in Patients with Systemic Lupus Erythematosus: A Cross-sectional Study from a Tertiary Care Centre of Eastern India

Internal Medicine Section

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ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) patients have an increased burden of atherosclerosis leading to adverse Cardiovascular (CV) events. Alterations in endothelial function, dysregulated immune system and increased oxidative stress are implicated in their development and progression. Carotid artery ultrasound is recommended to assess and follow progression of subclinical atherosclerosis and correlate with traditional/non traditional CV risk factors in SLE.

Aim: To study the correlation between Carotid Intima Media Thickness (CIMT), traditional/non traditional CV risk factors in SLE.

Materials and Methods: The hospital-based, descriptive, cross-sectional study was conducted in the Department of Internal Medicine, Medical College Kolkata, Kolkata, West Bengal, India, from April 2019 to August 2020. Patients with SLE, diagnosed by Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria, aged >12 years, irrespective of therapy status, were recruited by consecutive sampling. Subjects were classified as Lupus Nephritis (LN) and Lupus without Nephritis (LWN). Demographic data, parameters to define SLE (SLICC 2012 criteria), blood parameters like lipid profile, fasting plasma glucose, anti-Double stranded Deoxyribose Nucleic Acid antibody (anti-dsDNA Ab), C3/C4 levels, 24 hour urine protein values, haemoglobin, C-reactive Protein (CRP), serum homocysteine and Carotid Intima Media thickness as measured by Ultrasonography (USG) doppler study, duration of disease and medication history were considered as study variables. Statistical analysis was done by using Z-test, t-test, Analysis of variance (ANOVA), Chi-square test (for categorical data) and other non parametric statistical tests and correlation tests, wherever applicable. A p-value <0.05 was considered to be statistically significant.

Results: Fifty five SLE patients were studied. Subgroup analysis was performed between LN (n=36) and LWN (n=19). The mean age of the study subjects was 33 years with mean disease duration of 4.6 years. LN patients had longer disease duration, younger age of disease onset and longer duration of steroid usage. The mean systolic Blood Pressure (BP) was significantly higher in LN subgroup. Framingham Risk Scores (FRS) was positively correlated with duration of SLE disease and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) scores and duration of steroid therapy. The mean CIMT of the study population is 0.91 mm with 10.9% plaque prevalence whereas, mean CIMT of the LN subgroup and LWN subgroup was 1.02±0.27 mm and 0.86±0.3 mm, respectively; however no statistically significant difference in CIMT was observed between two subgroups. CIMT positively correlated with anti-dsDNA Ab levels, FRSs, anaemia, SLE Disease activity scores, 24 hour urine protein, duration of steroid usage, serum creatinine and CRP. No correlation between CIMT and age of subjects, Fasting Plasma Glucose (FPG), Triglycerides (TG) serum homocysteine was observed.

Conclusion: Systemic lupus erythematous patients have a high atherosclerosis burden and are at increased risk of adverse CV events. LN patients, early age of lupus onset, longer disease duration with prolonged steroid therapy, significant proteinuria, higher anti-dsDNA Ab levels and hypocomplementemia were observed to have higher mean CIMT and plaque formation.

Keywords: Cardiovascular risk, Carotid doppler ultrasonography, Endothelial dysfunction, Lupus nephritis, Prolonged steroid therapy

INTRODUCTION

Systemic Lupus Erythematosus (SLE), more commonly known as lupus is an autoimmune disorder that involves multiple organ systems with a wide variety of presentations. Symptoms can range from low-grade fever, joint pains, oral ulcers, photo sensitivity, blood dyscrasias, rash and chest pain. SLE patients are at high-risk for the development of premature atherosclerosis with a long period of subclinical evolution. With the rapid development of molecular biochemistry, pathophysiological mechanisms behind atherosclerosis in SLE are better understood. It includes endothelial cell dysfunction, vasculopathy and inflammation, along with traditional cardiovascular risk factors [1]. Cardiovascular diseases and infections are the main cause of death in SLE patients. In the Framingham Offspring study, it was found that the risk of a myocardial infarction is about 5-10 times higher in SLE patients even after traditional atherosclerotic risk factors were accounted for [2]. This risk was found to be even more pronounced in women with SLE aged 35-44 years, who were over 50 times more likely to have Acute Myocardial Infarction (AMI) than age/sex matched controls [2]. Dyslipidemia is the best studied complication of SLE leading to atherosclerosis in both young adults and paediatric population [3].

Insulin resistance has been shown to be present in adults with SLE and is a known independent risk factor for the development

of coronary artery disease [4]. Accelerated atherosclerosis, which leads to CV diseases, remains one of the most common causes of death in longstanding SLE patients. The Global Burden of Disease 2015 estimated a 12.5% rise in the number of deaths due to CV diseases, increasing from 15.9 million deaths in 2005 to 17.9 million deaths in 2015 even though the age standardised mortality rate (per 100,000) fell by 15.6% [5]. Hence, early detection of atherosclerosis changes is a key to achieve better long outcomes to decrease the CV morbidity and mortality from the ailment [6].

Subclinical atherosclerosis can be detected by using several modalities like measurement of Carotid Intima Media Thickness (CIMT) using carotid ultrasound, measuring the degree of coronary artery calcification by Computed Tomography (CT) scan and estimation of myocardial perfusion using Single Photon Emission Computed Tomography (SPECT). As recommended by the American Heart Association [7], measurement of CIMT, assessed by B-mode ultrasound at the carotid artery level is a widely accepted, inexpensive, easily accessible, non invasive measures to assess and follow subclinical atherosclerosis.

Pivotal studies have been conducted in this field. In the Rotterdam study and CV Health Study, higher CIMT and plaque was associated with 1.5 times and 1.8 times, (respectively) incidence of stroke over a follow-up period of five years [8,9]. Presence of plaque was associated with a 2.8-fold (Hazard ratio: 2.76, 95% Confidence interval: 2.1-3.63) increased risk of stroke, MI and CV death during a mean follow-up of 6.9 years in the Northern Manhattan Study (NOMAS) study [10]. When this was coupled with the Framingham Risk Scores (FRS) it had a better predictability in identifying high-risk populations. Hence, combination of traditional biomarkers along with vascular imaging, improves the risk stratification in patients.

In a single-centre case study, conducted in PGIMER, India across 100 SLE patients it was observed that LN patients tend to have more severe disease and greater vascular stiffness. CIMT was influenced by age, disease activity status and low High Density Lipid-Cholesterol (HDL-C) levels [11]. Bhatt SP et al., highlighted the younger age of incidence of SLE and in the present study, CIMT was influenced by age, disease activity, menopause, systolic blood pressure and total cholesterol, whereas the Systemic Lupus International Collaborating Clinics (SLICC) Albumin Creatinine Ratio (ACR) damage index was the sole factor affecting the plaque incidence [12].

There is a dearth of data, in Indian population, who are genetically and ethnically predisposed to premature atherosclerosis [13]. This study aimed to establish a correlation between surrogate biomarkers of subclinical atherosclerosis in SLE, as assessed by CIMT and their complex interplay with traditional and non traditional CV risk factors, which might help in risk stratification and timely initiation of specific therapy to reduce the morbidity and mortality in SLE patients.

MATERIALS AND METHODS

A hospital-based, descriptive, cross-sectional study was conducted in the Department of Internal Medicine, Medical College Kolkata, Kolkata, West Bengal, India, from April 2019 to August 2020. The ethical clearance was obtained from the Institutional Ethics Committee (approval no. MC/KOL/IEC/NONSPON/309/02-2019.) and a written informed consent was obtained from all the study subjects regarding their participation in the study.

Sample size calculation: On an average, it was observed from the hospital records that around 50 to 60 SLE patients (new and follow-up cases) attend the Internal Medicine/Rheumatology Outpatient Department (OPD)/Inpatient wards of the Institute, annually, hence, the technique of consecutive sampling was employed in this study.

Inclusion criteria: Patients who were >12 years and diagnosed with SLE as per the SLICC 2012 criteria [14], irrespective of the therapy status were included in the study.

Exclusion criteria: Individuals with history of diabetes, hypertension, dyslipidemia, Ischaemic Heart Disease (IHD), stroke or Transient Ischaemic Attack (TIA), lymphoproliferative disorder, carotid dissection surgery prior to the diagnosis of SLE, smokers or those infected with Human Immunodeficiency Virus (HIV) and who underwent head and neck radiation therapy, were excluded from the study.

Study Procedure

Parameters to define SLE (SLICC 2012 criteria), lipid profile, fasting plasma glucose, anti-dsDNA, C3/C4 levels, 24 hour urine protein values, haemoglobin, Erythrocyte Sedimentation Rate (ESR), serum homocysteine, carotid intimal media thickness as measured by Ultrasonography (USG) doppler study, duration of disease and medication history were considered as study variables.

A complete questionnaire with information on the patient's demographic profile, past medical history, drug history and psychosocial history were obtained from 69 individuals. Fourteen of them were excluded from the study as per the preset criteria and further laboratory and radiological evaluation was finally done among 55 study subjects. No patient was lost to follow-up. Laboratory parameters included evaluation of complete haemogram, fasting blood glucose, lipid profile, glycosylated haemoglobin (HbA1c), inflammatory markers like Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Liver Function Test (LFT), serum electrolytes, urea and creatinine. Autoimmune antibodies like Antinuclear Antibody (ANA), anti-dsDNA, complement levels were done to assess the disease severity. A 24 hour urine Albumin Creatinine Ratio (ACR) and routine urinalysis, were also performed.

Radiological analysis was performed to measure the bilateral carotid artery intimal thickness using the B-mode ultrasound scan at the Department of Radiology, Medical College and Hospital, Kolkata. The CIMT measurements were done at three levels on both sides- at the Common Carotid Artery (CCA) i.e., 10 mm caudal to the bulb of CCA; at the bulb of CCA and at the internal carotid artery (10 mm cranial to the flow divider). The mean and the maximum CIMT was calculated. The mean CIMT was defined as the average of all the three readings of CIMT on each side and "maximum CIMT" was defined as the maximum of all the six readings of CIMT assessed on a single subject. The following criteria were set for the further analysis of CIMT measurement and its correlation with existing biomarkers of subclinical atherosclerosis [Table/Fig-1] [15].

CIMT (mm)	Interpretation
<0.9	Normal
0.9-1.3	Thickened
>1.3	Atherosclerotic plaque

[Table/Fig-1]: Interpretation of Carotid Intimal Media Thickness (CIMT) measurement based on ultrasonographic assessment [15].

The results of the study were further categorised to assess the difference in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score and the CV risk factor using Modified Framingham Risk Score (mFRS) [16,17].

STATISTICAL ANALYSIS

The data was appropriately segregated, categorised and were entered into IBM Statistical Package for the Social Sciences (SPSS) software version 16.0. They were double checked for any error while data entry. Comparisons were analysed using Z-test, t-test, Analysis of Variance (ANOVA), Chi-square test (for categorical data) and other non parametric statistical tests, correlation tests wherever applicable. An alpha level was set at 5% and a p-value <0.05 was considered statistically significant. The power of the study was 80%.

RESULTS

Out of the 55 study subjects, 53 were females (96.36%) and two were males (3.64%). The mean age and Body Mass Index (BMI) of the study population was 33±5 years and 22.6±1.98 kg/m^2, respectively. It was found that 19 (34.54%) patients had Lupus with Nephritis (LN) whereas, 36 (63.46%) patients with Lupus without Nephritis (63.46%) (LWN) as their presenting features. The demographic profile of the study subjects are described as shown in [Table/Fig-2].

Variables	LN	LWN	Total
Distribution of age (in years)			
12-30	4	16	20
31-48	15	18	33
>48	0	2	2
Total	19	36	55
Mean±SD age in years	35.16±5.39	31.92±6.55	
Gender distribution			
Male	0	2	2
Female	19	34	53
Total	19	36	55
Duration of disease (years) (Mean±SD)	5.79±3.23	4.06±3.70	**p-value** 0.078
BMI (kg/m^2) (Mean±SD)	22.69±2.16	22.47±1.62	0.698
Systolic blood pressure (mm Hg) (Mean±SD)	146.00±18.607	128.72±18.573	0.002*

[Table/Fig-2]: Demographic profile of the study subjects.
LN: Lupus with nephritis; LWN: Lupus without nephritis; SD: Standard deviation.
*p-value <0.05 was considered statistically significant

Further parameters of the study were analysed by comparing them in patients with nephritis and without nephritis. The laboratory and clinical parameters of the study subjects with LN and LWN are shown in [Table/Fig-3] as follows. The results of the study were further categorised to assess the difference in the SLEDAI-2k score and the CV risk factor using mFRS. Although no significant difference was observed in the latter, SLEDAI-2k score was significantly higher (26.79±4.59, p-value=0.001) in subjects with LN as shown in [Table/Fig-4]. Parametric analysis between the SLEDAI-2k and mFRS revealed a significant level of association.

Parameters	LWN (N=36)	LN (N=19)	p-value
Haematological parameters			
Haemoglobin (g/dL)*	10.34±1.61	9.26±1.23	0.014*
Total leucocyte count (in per cu.mm)	6441.56±2856.08	5354.32±2238.03	0.156
Platelet count (lakhs per cumm)	1.92±0.63	1.59±0.46	0.054
ESR (mm/hour)	37.25±8.30	41.21±5.76	0.08
Serological parameters			
LDL cholesterol (mg/dL)	115.00±26.195	110.95±20.90	0.568
Total cholesterol (mg/dL)	188.94±29.92	190.68±30.982	0.84
Triglyceride (mg/dL)	181.36±27.280	197.26±35.66	0.071
HDL cholesterol (mg/dL)	37.36±3.05	36.32±3.75	0.27
Fasting plasma glucose (mg/dL)	105.58±15.01	114.21±20.97	0.084
Urea (mg/dL)	28.58 ±7.29	38.32±17.73	0.006*
Creatinine (mg/dL)	1.12±0.31	1.41±0.46	0.009*
C-reactive protein (mg/L)	10.58±5.44	15.11±7.51	0.013*
Serum C3 levels (mg/dL)	103.39±30.08	82.21±14.71	0.006*
Serum C4 levels (mg/dL)	16±14.98	16±14.09	1
Anti-dsDNA Ab (IU/mL)	167.97±104.14	274.21±232.94	0.023*
Urinalysis			
24 hour urine protein (mg/day)	689.56±470.76	1634.00±900	0.001*

[Table/Fig-3]: Laboratory and clinical parameters.
LN: Lupus with nephritis; LWN: Lupus without nephritis; SD: Standard deviation; ESR: Erythrocyte sedimentation rate; LDL: Low density lipoprotein; HDL: High density lipoprotein; dsDNA Ab: Double stranded deoxyribose nucleic acid antibody.
*p-value <0.05 was considered statistically significant

Parameters	LWN (n=36)	LN (n=19)	p-value
Modified Framingham Risk Score (%)	2.272±2.1515	4.621±3.5659	0.948
SLEDAI-2k	4.544±4.3029	26.79±4.590	0.001*

[Table/Fig-4]: Analysis of Modified Framingham Risk Score and SLEDAI-2k score in study population.
LN: Lupus with Nephritis; LWN: Lupus without Nephritis; SD: Standard Deviation.
*p-value <0.05 was considered statistically significant

The radiological parameters that were assessed using carotid doppler were analysed and it revealed notable results. The mean CIMT of the study population (N=55) was detected to be 0.91±0.3 mm. Twenty three (41.81%) patients had non thickened carotid intima media (≤0.9 mm) whereas, 32 (51.19%) patients had thickened carotid intima (>0.9 mm). Out of the 32 patients, 6 (18.75%) of them had atherosclerotic plaque. Plaques were observed among three LN, two neuropsychiatric SLE and one SLE with APS patients. The CIMT levels were subgrouped on the basis of age, as shown in [Table/Fig-5]. CIMT levels were not influenced by the age of the patients and it was observed that the six patients, who had atherosclerotic plaque were >30 years of age. The CIMT was influenced by the duration of the disease and it was seen that 45% of the patients, who had the disease for less than five years and 77% patients with disease duration ≥5 years had thickened CIMT (>0.9 mm). The results were statistically significant with a p-value of 0.048 as shown in [Table/Fig-6]. No correlation was observed between mean CIMT and serum homocysteine levels and fasting plasma glucose in the present study.

Age (years)	Carotid intima media thickness: Non Thickened (<0.9 mm) (n=23)	Thickened (0.9-1.3 mm) (n=26)	Thickened (>1.3 mm) (n=6)	Total (n)
12-30	8	11	0	19
>30	15	15	6	36

[Table/Fig-5]: Distribution of Carotid Intima Media Thickness (CIMT) with age.
p-value=0.145

Parameters		Carotid intima media thickness: Non thickened (<0.9 mm)	Thickened (0.9-1.3 mm)	Thickened (>1.3 mm)	Total	p-value
Duration of disease (years)	<5	18	13	2	33	0.048*
	≥5	5	13	4	22	
Total		23	26	6	55	
Duration of steroid therapy (years)	<1	14	6	1	21	0.013*
	1-5	8	18	3	29	
	>5	1	2	2	5	
Total		23	26	6	55	
Body mass index (kg/m^2)	Normal (18.5-22.9)	13	13	1	27	0.034*
	Overweight (23-24.9)	4	10	5	19	
	Obese (>25)	6	3	0	9	
Total		23	26	6	55	

[Table/Fig-6]: Distribution of Carotid Intima Media Thickness (CIMT) of the study subjects with respect to the duration of the disease, duration of steroid therapy and BMI.

A statistically significant association was seen between LDL-C and mean CIMT. Interestingly, it was noted that 70% of the individuals with a low HDL-C had thickened CIMT or plaque formation. The distribution of serum LDL-C, HDL-C, CRP and serum C3/C4 levels among study subjects with variable levels of CIMT are shown in

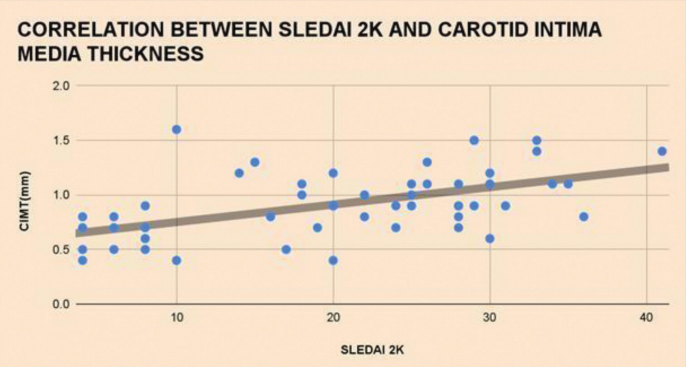
[Table/Fig-7]. The evidence of severity of the disease was reflected by hypocomplementemia, anti-dsDNA Ab levels and SLEDAI-2k scores, and it was compared with the mean CIMT levels to establish association. It was observed that 76% study subjects with hypocomplementemia had thickened CIMT or plaque formation [Table/Fig-7]. Similarly statistically significant difference between Anti-dsDNA Ab levels with mean CIMT (p-value=0.001) was observed. When analysing the SLEDAI-2K score for SLE, it was found that 27 patients had a score >20. Among them, 21 (77.78%) had either thickened intima or plaque formation as shown in [Table/Fig-8]. Statistical testing showed a positive correlation and significant association of SLEDAI-2K score and CIMT (r-value=039, p-value=0.01) as shown in [Table/Fig-9]. The positive correlation can be explained by the fact that, patients with longer duration of disease tend to accrue disease damage and therapy related complications over time.

Parameters		Carotid intima media thickness: Non thickened (<0.9 mm) (n=23)	Thickened (0.9-1.3 mm) (n=26)	Thickened (>1.3 mm) (n=6)	Total (n)	p-value
LDL-C (mg/dL)	<130	21	20	2	43	0.009*
	>130	2	6	4	12	
HDL-C (mg/dL)	<40	12	22	6	40	0.011*
	>40	11	4	0	15	
CRP (mg/L)	<10	11	6	0	17	0.039*
	>10	12	20	6	38	
C3 levels (mg/dL)	<90	6	15	4	25	0.046*
	>90	17	11	2	30	
C4 levels (mg/dL)	<10	6	15	4	25	0.046*
	10 to 40	17	11	2	30	

[Table/Fig-7]: Distribution of serum LDL-C, HDL-C, CRP and C3/C4 among study subjects with variable levels of carotid intima media thickness.
LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; CRP: C-reactive protein.
*p-value <0.05 was considered statistically significant

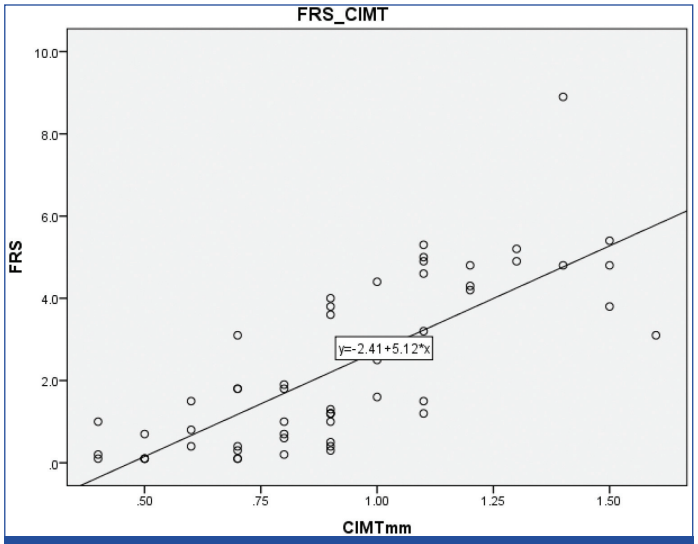
SLEDAI-2k score	Carotid intima media thickness: Non thickened (<0.9 mm)	Thickened (0.9-1.3 mm)	Thickened (>1.3 mm)	Total
4 to 20	17	10	1	28
>20	6	16	5	27
p-value-0.010*				

[Table/Fig-8]: Distribution of carotid intima media thickness of the study subjects with respect to the SLEDAI-2k score.



[Table/Fig-9]: Pearson's correlation curve showing a linear association between carotid intima media thickness and SLEDAI-2k with r-value=0.39, p-value=0.01.

Also, while analysing the treatment history of the patients and the duration of steroid therapy, it was found that 29 (52.72%) participants had been receiving the treatment for 1-5 years and 5 (9.1%) subjects for more than five years. Twenty one of the 29 subjects (72.41%) and 4 (80%) out of five subjects had thickened intima or plaque formation in the respective subgroups. A statistically significant relation between duration of steroid therapy (years) with the mean CIMT exists as p-value was 0.013 as shown in [Table/Fig-5]. Individuals with higher FRSs were observed to have plaques and thickened carotid intima media (as shown in [Table/Fig-10]) as shown by Pearson's Correlation curve.



[Table/Fig-10]: Pearson's correlation curve showing a linear association between cIMT and mFRS with r-value=0.765 and p-value <0.001.

In the present study, CIMT was positively influenced by higher disease activity scores, longer duration of steroid usage, younger age of disease onset, presence of dyslipidemia and hypertension and LN. This outlines the fact that CIMT in conjunction with other biomarkers can estimate CV risk in SLE patients.

DISCUSSION

There is a complex interplay of diverse factors like genetics, immunogenicity, endothelial dysfunction and immune complex formation that lead to subsequent tissue damage in SLE. The natural course of the disease is characterised by phases of remission and exacerbation with intervals between flares varying considerably [18]. Nevertheless, cumulative damage worsens with time and impacts patient prognosis. Mortality is bimodal with an early peak in the first years after diagnosis due to disease activity and/or infections and a later peak due to premature atherosclerotic CV events and organ failure [19]. The events of atherosclerosis remain undetected due to asymptomatic nature of presentation in the early days. The subclinical events can be ascertained with the help of certain non invasive modalities like CIMT, FMD using B-mode ultrasonography, at the level of the carotid artery.

Carotid intima media thickness value in the present study did not significantly vary among the subgroups of LN and LWN which is similar to an Indian study [11]. However, the SLEDAI-2K was significantly higher in LN when compared to LWN in the present analysis. The SLEDAI-2k is a widely used scoring scale for the disease activity in SLE, that points out the disease burden. It is ingrained in clinical practice now-a-days, due to its simplicity to score and predict future outcomes [20]. It was observed that the plaque formation in SLE is significantly associated with serum inflammatory markers like CRP, C3 complement levels, duration of disease and steroid therapy. In a prospective study, conducted by Belibou C et al., on 35 female subjects, concluded that significant association exists between CIMT and duration of SLE (r-value=0.460), High-sensitivity C-reactive Protein (hsCRP) (r-value=0.436), as well as, SLEDAI-2k score (r-value=0.466) and a positive correlation with FRSs. The modified CIMT (mCIMT) observed (0.89 mm) is similar to the present study [21].

In a study conducted at the University of Pittsburgh among 214 female patients with SLE, there was a focal plaque prevalence of

32% with CIMT (mean±SD) being 0.71±0.1 mm. They concluded that, the risk factors associated with CV disease in SLE is primarily due to vascular stiffening and is positively correlated with high SBP, old age and higher C3 levels [22]. A similar finding in the present study was seen in which the plaque prevalence is 51.19% with mean IMT as 0.91±0.3 mm. Logistic regression in a study conducted by Manzi S et al., on 175 Caucasian patients concluded that the presence of plaque is independently associated with older age, longer duration of disease and prolonged duration of steroid therapy [2]. Similarly, the study by Colombo BM et al., shows that age plays a significant factor in cases of LN: however in the present study, no correlation was observed between age of subjects and mean CIMT [23]. This is similar to the findings of a prospective cohort study conducted by Doria A et al., among 78 subjects [24]. The latter study also made another interesting observation, that cumulative prednisone dose is an important non traditional risk factor for accelerated atherosclerosis. Cumulative prednisone dosage is known to be a double edged sword with proinflammatory and anti-inflammatory properties being displayed at varying dosages. Roman MJ et al., observed that the average dose of prednisone was significantly less in patients with carotid plaque in current/past users, concluding that there may be a threshold dose where the anti-inflammatory effects of glucocorticoids may be athero-protective, beyond which doses may be atherogenic [25]. A study done by Manzi S et al., has shown a positive correlation between duration of steroid usage and higher CIMT values, similar to the present study [2].

In a case-control study, among 197 patients with lupus the plaque prevalence was higher than the 197 matched controls (37.1% vs 15.2%, p-value <0.001) [25]. The multivariate analysis concluded that the duration of disease, damage index score and absence of anti-smith antibodies are independent predictors of the disease, whereas no positive correlation was found between mCIMT and serum homocysteine levels. Dyslipidemia is observed in a high frequency in patients with LN. Most patients have high total Cholesterol and one in every third patient have high LDL levels along with low HDL levels, as was concluded by Sajjad S et al., [26]. It is in congruence with the findings of thickened intima media in patients with deranged lipid profile in the present study.

Among the South Asian population, Sharma SK et al., observed a mCIMT of 0.54 mm and an inverse relationship between severity of anaemia and CIMT [11]. LN patients tend to have lower mean haemoglobin values (9.96 mg/dL) compared to non LN patients. This can be attributed to the higher disease activity in LN patients, formation of anti-erythrocyte antibodies, anaemia of chronic disease due to circulating TNF-alpha and cytokines, nutritional deficiency, iron deficiency anaemia, autoimmune haemolytic anaemia and Gastrointestinal (GI) blood loss due to prolonged steroid usage in LN patients, although no significant difference was obtained between CIMT of LN patients and those without nephritis [11]. Bhatt SP et al., made an observation in their study regarding the younger age of onset of SLE in Indians, who exhibited features of atherosclerosis, even with low disease activity [12]. Median age of patients was 30 years, CIMT in patients was 0.417±0.07 mm, as compared to 0.362±0.07 mm in controls, whereas, plaques were noted in 14% patients. CIMT was influenced primarily by age, disease activity, systolic blood pressure and total cholesterol, whereas the SLICC ACR damage index was the sole factor affecting the plaque incidence.

In a study conducted by Ghosh P et al., a case control study with 60 SLE patients and 38 controls were taken [27]. Mean age of the patients was 31 years, the CIMT was higher in patients (mean 0.49±0.08 mm), compared to controls (0.39±0.05 mm). SLE damage indices were independent predictors of CIMT. The difference with the above studies in observed mean CIMT values could be due to difference in sample size, SLE type subsets, cut-off values for defining thickened CIMT and observer variations. The higher mean carotid intima values in the present study can be due to average duration of disease being higher, presence of hypertension and individuals with impaired fasting glucose as co-morbidity, more number of LN patients, high fraction of patients with higher SLE disease activity scores, longer duration of steroid usage. Individuals with higher FRSs were observed to have plaques and thickened carotid intima media, higher disease activity scores, longer duration of steroid usage, younger age of disease onset, presence of dyslipidemia and hypertension and LN, findings echoed by studies conducted by Zhang M et al., [28].

In view of this, laboratory markers like homocysteine, CRP, lipid profile and SLE disease specific factors and carotid intima media assessment by USG doppler study may be used to design a model to predict CV risk in SLE patients, and it may gain more acceptability, reproducibility across various age groups, population, racial subtypes and spectrum of co-morbidity, which can then be utilised for risk stratification of SLE patients, to guide the initiation of disease modifying drugs, assessing therapy response and help in amelioration of disease related damage and risk factors.

Limitation(s)

Firstly, it was a cross-sectional, single-centre study with a small target population. The CIMT, which was the secondary point of the present study, was measured using doppler imaging. It is observer dependent and results can be subjective. The drug effects and role of genetics that, might influence the results are not considered in detail. These are the elements, that challenge the external validation of the study.

CONCLUSION(S)

The SLE patients have a high atherosclerosis burden and are at increased risk of adverse CV events. The present study demonstrated the increased disease severity in patients with LN, which may help to fill the gaps in the existing literature on the association of CIMT with hypocomplementemia, degree of dyslipidemia and prolonged steroid use. However, more evidence-based researches are required on this field, to establish a causal relationship in understanding the implication of the disease and its effects.

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