

Endothelial Dysfunction in Systemic Lupus Erythematosus

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Abstract: Despite improved prognosis, patients with systemic Lupus, remain at increased risk of early vascular events due to premature atherosclerosis. We assessed the endothelial dysfunction in SLE as a marker of early atherosclerosis.

In thirty seven (37) female patient endothelial dependant vasodilatation (EDD) was assessed at the brachial artery in response to shear stress and glyceril trinitrate administration (NMD), intima media thickness of the common carotid artery was also measured using high resolution B-Mode ultrasonography., anticardiolipin antibodies (done only in 18 patients) Lipid profiles, ANA were also assessed.

No statistically significant difference between patients and control in basal FMD (D₁) (P=0.5) or percent change in flow mediated dilation (D₂) P = 0.3 and no change in NMD (P = 0.2).

There was weak but statistically significant correlation between FMD% and NMD% (r = 0.3, P = 0.05). Despite the disease activity according to SLEDAI (where 45.9% of patients were severely active) there was no correlation between either disease activity and FMD (r = 0.03, P = 0.8), or disease duration (2.4±3.3 years) (r = 0.7, P = 0.8) Weak but statistically significant negative correlation between hypercholesterolemia and endothelial dysfunction (r = 0.3, P = 0.05). We tried to find differences between patients themselves dividing them into those with FMD <10% (n = 23 patient, 62.2%) FMD ≥ 10% (n = 14 patient, 37.8%) or FMD %/ NMD % < 0.7 (n = 23 patient, 62%), FMD % /NMD > 0.7 (n = 14 patient, 38%). However no significant differences between them as regard clinical and laboratory data.

In conclusion, FMD was not different between patients and control thus its use as a predictor of future cardiovascular events is questionable.

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1. Introduction

Patients with systemic lupus erythematosus are still at considerable risk for premature death due to accelerated atherosclerosis as traditional risk factors alone cannot explain the increased prevalence of atherosclerosis (1)

The natural history of the initial vascular complications in patients with SLE is multifactorial auto antibodies, immune complexes and cytokines play a major role in favouring endothelial dysfunction (2)

Thus the possibility to detect early vascular damage for early prevention strategies, management and treatment of the disease will thus positively influence outcome.

Endothelial function can be assessed with a well validated non –invasive technique using ultrasound to detect the vasoreactivity of the brachial artery to shear stress (flow mediated dilation (FMD) or to nitroglycerine (Nitro-glycerine mediated dilatation) NMD).

Conflicting data have been reported concerning the correlation between endothelial dysfunction and FMD.

Aim of the present study was to evaluate the efficacy of FMD in early detection of endothelial dysfunction in patient with SLE.

2. Patients and Methods:

Thirty seven patients (Female/Male = 33/4) mean age (24.1±7.6 years) chosen from Kasr El Aini University Hospital, Internal Medicine Department and Rheumatology Clinic fulfilling at least 4 of the update revised criteria of the American College of Rheumatology for SLE diagnosis (3)

The study was conducted from January 2009 to May 2010. Compared to 10 healthy female volunteers with mean age (24.4±8.5). A verbal consent was obtained from all subjects participating in the study after explaining its nature. Disease activity was evaluated at the beginning of the study using SLE disease activity index (SLEDAI). (4)

All patients underwent detailed medical history, complete physical examination detailed history of drug intake, BMI. Patient with diabetes, BMI ≥ 30 and smokers were excluded.

All sera after 12-14 hour fast were tested for cholesterol, triglycerides, AST, ALT, albumin were done on automated analyzer Hitachi 917;commercial

kits were supplied by Roche diagnostics(Boehringer Mannheim,Germany)ESR was evaluated by westergren method.24 hour urinary protein,C₃,C₄ were measured by immunonephelometric method supplied by (Siemens,Deerfield,USA)Antinuclear Antibodies were determined using immunofluorescence testing on HEP2-cells.Anti Double stranded DNA antibodies ,Anti cardiolipin antibodies were detected by ELISA kits (Nunc,Denemark)and (Sumilon,Tokyo)respectively.

Assessment carotid IMT

Doppler ultrasound was done for all patients and control subjects to asses FMD and carotid intima media thickness (CIMT).

Colour-coded carotid duplex sonography was performed in all subjects in the supine decubitus position, during gentle respiration. The study was carried out by the same operator using a high-resolution B-mode ultrasonography (Philips HDI 5000 SONOCT with a 7-12 MHz linear –array transducer) placed on the patient neck with the least possible pressure in order not to compress the overlying jugular vein and allow expansion of the carotid artery in all directions. The carotid view was achieved in longitudinal scan on the extra-cranial artery segment at 1 cm from the common carotid bulb (5).The IMT was defined as the distance between the leading of the luminal echo to that of the media/adventitia echo.IMT <0.8mm (0.4-0.7 mm) was defined as normal (6) and plaque was defined as a localized thickening of at least 1.2 mm that does not uniformly involve the artery (7)

Assessment of FMD:

Participants lay in a supine position and sphygmomanometer cuffs were applied on arm just above the level of elbow.

The right brachial artery was assessed using high-resolution B-mode ultrasound (Philips HDI 5000 SONOCT linear broad band 7-12 MHZ transducer) after the published protocol (8)

1-Endothelium-dependent FMD:

Follow a 2-min baseline period, a frozen 3-cm longitudinal image of the vessel without colour flow was obtained and frozen for 5s.

A pneumatic tourniquet placed around the forearm proximal to the target artery (upper arm occlusion) was inflated after the baseline phase to a pressure of 50 mm Hg above the subject systolic blood pressure (or until no blood flow was noticed through the brachial artery by the Doppler probe), and this pressure was held for 5 min.Increased flow was then induced by sudden cuff deflation.

A continuous scan was performed at deflation, 60 and 90s after cuff deflation, with frozen

and Doppler measurements recorded at similar intervals to the baseline phase.

2-Nitroglycerin (NTG)-induced (non-endothelium dependent) FMD:

NTG acts as a positive control by inducing vascular smooth muscle dilation independently of endothelial function.

Thirteen minutes after cuff deflation, a second 2-min baseline resting scan was recorded to confirm vessel recovery. After the administration of sublingual NTG tablet, scanning was performed continuously for 5 min.

3-Data analysis:

The diameter of the brachial artery was measured from the anterior to the posterior interface between the media and adventitia (m line) at a fixed distance .The mean diameter was calculated from four cardiac cycles synchronized with the R-wave peaks on the electrocardiogram.

All measurements were made at end diastole to avoid possible errors resulting from variable arterial compliance.

FMD at 5min post-ischemia (100x diameter (5min after deflation of cuff)—Diameter (basal)/ Diameter (basal).

In addition, nitroglycerine-mediated dilation (100x Diameter (after nitroglycerine) Diameter (basal)/Diameter (basal) was used to represent endothelial independent vasodilatation (9)

The diameter percent change caused by endothelium-dependent flow-mediated vasodilatation (%FMD) and endothelium-independent percent change from baseline in NTG-mediated vasodilatation (%NTG) were expressed as the percent change relative to that at the initial resting scan. Significant endothelial dysfunction was defined as FMD<10% and NMD>10 % (10)

In order to increase the sensitivity and specificity of the technique FMD/NMD <0.7 defined endothelial dysfunction (11)

4. Statistical Methodology:

Statistical package for social science (SPSS) program version 9.0 was used for analysis of data. Data was summarized as mean, SD. Non parametric test (Mann Whitney U) was used for analysis of two quantitative data.

One way ANOVA was done for analysis of more than two variables followed by post Hock test for detection of significance.

Simple linear correlation (Pearsons correlation for quantitative data was done to detect the relation between D1D2x100 andD3D1x100 with all other dermographic and laboratory data.

3. Results:

Thirty seven SLE participants characteristics shown in table (1) Mean disease duration in years

2.4±3.3, sex distribution F/M=33/4. 10 control subjects were studied. (Mean age: 24.4±8.5 years) Disease activity using (SLEDAI) inactive (n=6, 16.2%), mild activity (n=5, 13.5 %), moderate activity (n= 9, 24.3%) severe activity (n=17, 46%) History of Reynaud's (n=4, 10.8%),cerebrovascular stroke (n=4, 10.8%) no deep vein thrombosis ,no history of vasculitis, pulmonary embolism or other thromboses .Steroids used by all patients mean duration (2.4±3.3years),mean dose (21.9±22.5), chloroquine was used in (n=13, 35.1%) mean duration (2.6±21 year) mean dose 250 mg.Azathioprine was used in (n=4, 10.8%) ,mean duration (3.5±2.1 year) mean dose 100mg. ANA (n=31, 16.3%) ADNA (n=24, 64.9%) Anticardiolipin IgM (n=6, 33.3%) IgG (n=4, 22.2%).

Table 1: Difference between SLE patients and controls as regards demographic, anthropometric, and clinical & laboratory findings:

Variables	Patients n=37		Control n=10		P-value
	Range	Mean ± SD	Range	Mean ± SD	
Age (yrs)	15.0-50.0	24.1 ±7.6	15.0-43.0	24.4 ±8.5	0.9
SBP(mmHg)	100-140	117.2±11.7	100-130	118.0 ±9.2	0.7
DBP(mmHg)	60 -90	74.5 ±8.5	60 -90	77.5 ±8.6	0.3
Wt (Kg)	56.0-89.0	66.5 ±7.5	56.0-73.0	62.2 ±5.6	0.08
Ht(m)	1.6-1.8	1.6 ±0.06	1.6-1.7	1.6 ±0.03	0.09
BMI (Kg/m ²)	19.5-29.2	24.9 ±2.2	21.8-26.8	24.3 ± 1.5	0.4
Dis.dur. (yrs)	0.02-18.0	2.4 ±3.3	-	-	-
RBS (mg/dl)	53.0-131.0	86.5 ±22.2	50-114	82.6 ±22.0	0.7
T. chol. (mg/dl)	100-343	199.1 ±69.5	105-204	159.1 ±39.0	0.1
TG (mg/dl)	59-721	210.7±166.0	90-205	133.0 ±36.0	0.5
Hb (gm/dl)	4.5-15.9	9.2 ±2.2	9.0-12.0	10.5 ± 1.1	0.03*
TLC (mm ³)	2.3-1.1	2.4 ±3.3	3.2-10.4	6.3 ±2.4	0.008*
Lymph, count	100-5000	1316.2 ±1022.4	1400-3000	1915 ±493.3	0.01*
Platelet (mm ³)	61.0-565.0	255.5±160.2	155-350	230.0±64.4	0.7
AST (IU/ L)	11.0-290.0	49.8 ±55.6	13-43	25.1 ± 10.5	0.1
ALT (IU/L)	10-175	39.2 ±36.7	17.0-47.0	25.6 ±8.9	0.7
S.Albumin(gm%)	2.1-4.7	3.3 ±0.8	3.3-4.4	3.9 ±0.3	0.02*
S.Creat. (mg/dl)	0.3-5.5	1.3 ± 1.2	0.3-1.1	0.8 ±0.3	0.1
U.ptn(gm/24hr)	0.1 -3.7	0.9 ± 1.1	-	-	-
ESR1(mm/hr)	10-140	101.1 ±40.2	5.0-11.0	6.8 ±2.3	0.0001*
ESR2(mm/hr)	25-147	91.2±36.2	7.0-18.0	11.9±3.5	0.001*

*p<0.05 significant

Table (2) show no statistically significant difference between SLE cases and control as regards FMD

considered as basal dilatation (p=0.5) or percent dilatation (p=0.3) or percent NMD (p=0.2).No significant difference as regards IMT between patients and control.(fig 2)

Table 2: Comparison study of the Doppler examination data between patients and controls:

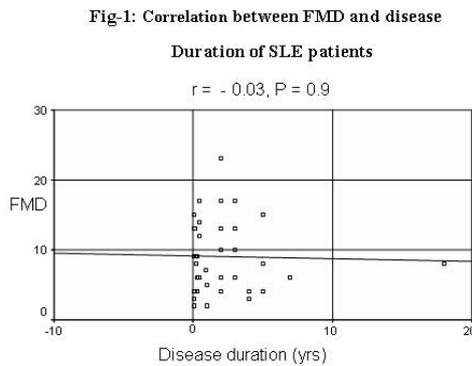
Variables	Patients		Control		P-value
	Range	Mean ± SD	Range	Mean ± SD	
Basal diameter [D1]	0.22-0.47	0.3 ±0.1	0.29-0.33	0.3 ±0.01	0.5
Absolute FMD [D2]	0.23-0.48	0.3 ± 0.1	0.31 -0.38	0.3 ± 0.03	0.3
Percent FMD [D2-D1/D1X100]	2-23	9.0 ±5.1	3-18	10.7±4.5	
Absolute NMD [D3]	0.25-0.51	0.4 ±0.1	0.34-0.39	0.4±0.02	0.2
Percent NMD [D3-D1/D1X100]	4-29	15.6±6.1	12.0-24.0	17.9 ±3.4	
CIMT	0.3-0.6	0.4 ±0.07	0.3-0.5	0.5 ±0.07	0.8

Table (3) show Comparative study between patients with FMD %<10 n=23, and FMD% ≥10 n=14, where there was no statistically significant difference between them as regards any clinical, laboratory data ,disease activity .

Table 3: Comparative study between patients with FMD %< 10 n=23, and FMD% ≥10 n=14

Variables	patients		P-value
	FMD<10 Mean ± SD N = 23	FMD > 10 Mean ± SD N= 14	
Age (yrs)	24.5 ± 8.3	23.5 ±6.4	0.9
Disease duration. (yrs)	2.7 ±4.0	2.0 ± 1.6	0.7
Ster. Duration (yrs)	2.7 ±4.0	2.0 ± 1.6	0.7
Steroid dose	23.4 ±24.5	19.2 ± 19.2	0.9
SBP (mmHg)	115.9 ± 10.3	119.3 ±3.8	0.5
DBF (mmHg)	73.3 ± 8.5	76.4 ±8.4	0.4
Wt(Kg)	65.3±6.1	68.3±9.3	0.4
Ht (m)	1.6±0.05	1.7 ±0.06	0.1
BMI (Kg/m ²)	25.0 ±2.3	24.8 ±2.0	0.6
SLEDAI score	10.2 ±7.0	9.9 ±7.7	0.8
RBS (mg/dl)	88.0 ±24.8	84.0 ± 17.8	0.7
T. chol (mg/dl)	209.6 ±69.9	191.9 ±67.8	0.2
TG (mg/dl)	219.4 ± 188.8	196.4 ± 125.2	0.8
CIMT	0.05 ±0.008	0.05 ±0.005	0.8
Hb (gm/dl)	9.7 ±2.3	8.4 ± 1.9	0.2
TLC (mm ³)	2.1 ±3.1	2.8 ±3.6	0.9
Platelet (mm ³)	269.8 ± 149.1	221.2 ± 198.7	0.5
AST (IU/ L)	49.7 ±58.8	50.0 ±5.1	0.9
ALT (IU/L)	40.0 ±34.2	37.8 ±41.9	0.8
S.Alb.(mg/dl)	3.2 ±0.7	3.3 ±0.8	0.7
S.Creat(rng/dl)	1.3 ± 1.3	1.4 ±0.9	0.4
U.ptn(gm/24hr)	1.0 ± 1.2	0.8 ±0.8	0.7
ESR1	97.2 ±42.5	107.5 ±36.7	0.7
ESR2	79.1 ±26.8	106.7 ±42.7	0.06

Figure (1) shows no significant correlation between FMD and disease duration $p=0.9$, $r=-0.3$



To increase the specificity and sensitivity of the Doppler study Comparative study was done between patients with FMD/NMD <0.7 and those with FMD/NMD ≥0.7 as regards different clinical and

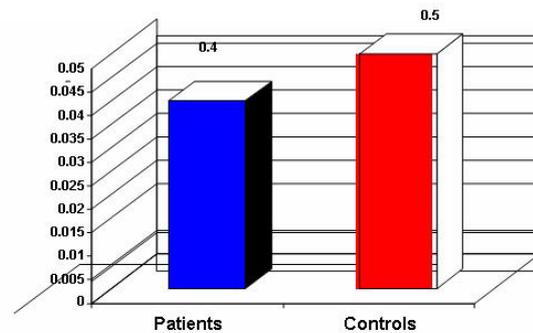
Laboratory data, however no statistically significant difference was found (Table-4).

Table 4: Comparative study between patients with FMD/NMD <0.7 and those with FMD/NMD ≥0.7 as regards different clinical and Laboratory data.

	FMD / NMD < 0.7 N = 23		FMD / NMD ≥ 0.7 N = 14		P-value
	N	%	N	%	
Sex: Males	2	8.7	2	14.3	0.5
Females	21	91.3	12	85.7	
Recurrent abortion	1	33.3	0	0	0.6
HTN:	1	4.3	1	7.1	0.5
Reynaud's:	2	8.7	2	14.3	0.3
Fever :	10	43.5	4	28.6	0.3
Oral ulcer :	10	43.5	4	28.6	0.3
Malar rash :	8	34.8	3	21.4	0.6
Photosensitivity:	6	26.1	4	28.6	0.3
Alopecia:	7	30.4	8	42.9	0.4
Discoid rash :	3	13	3	21.4	0.5
Puffy eve :	9	39.1	6	42.9	0.02*
Pallor :	4	17.4	8	57.1	0.5
Vasculitis :	2	8.7	2	14.3	0.3
CNS :	2	8.7	3	21.4	0.2
Arthritis :	7	30.4	2	14.3	0.6
Serositis :	1	4.3	1	7.1	0.5
Weight loss :	7	30.4	5	35.7	0.5
Lower limb edema:	9	39.1	6	42.9	0.7
DVT:	2	8.7	1	7.1	0.5
ANA :	10	43.5	6	42.8	0.7
Positive					
ADNA:	9	39.1	5	35.7	0.6
Positive					
ACL IgG:	4	36.4	0	0	0.1
Positive					
ACL IgM:	5	45.5	1	14.3	0.2
Positive					

Weak but statistically significant negative correlation between hypercholesterolemia and endothelial dysfunction($r=-0.3$, $p=0.05$) was found.

Fig 2 : Comparison between patients and control as regards CIMT



4. DISCUSSION

This study shows normal endothelial function as assessed by FMD either absolute or percent dilatation in a population with SLE.

This finding is in striking contrast to prior studies which have reported blunted FMD in S.L.E. (11), (12), (13). (14)

The reason for this discrepancy may be due to application of the cuff of sphygmomanometer proximally where the more proximal arterial occlusion is known to produce a stronger shear stress stimulus which may be related to recruitment of more resistance vessels (8) leading to the production of significantly greater hyperaemic and vasodilatory responses (15).

Lima et al, Found reduced FMD in SLE patients even without coronary heart disease, but NMD was reduced only in anticardiolipin positive patients, Mean ±SD of FMD in SLE was 5.0±5% compared with 12.0±6.0% in healthy control subject's .In that study, postmenopausal women and subjects with known CHD risk factors were excluded (Lima et al (14).

Also El- Magadmi, et al., found that SLE patients were significantly associated with impaired FMD (P=0.017) (12)

Kiss, et al., 2006, reported that the endothelium dependent vasodilatation (FMD) was significantly impaired in SLE patients as compared to controls. The absolute difference of vessel diameter after shear stress was 0.25±0.15 mm in patients vs.0.38±0.16 mm in controls (p=0.001) and as in percent of the rest diameter FMD % was 7.31±5.2% inpatients vs. 9.86±3.87% in controls (p=0.013) however NMD did not differ (16).

However in our study ,the absolute difference of vessel diameter after shear stress was $0.3 \pm 0.1\%$ mm in patients vs. 0.3 ± 0.03 mm in controls) and as in percent of the rest diameter (FMD%) was $9.0 \pm 5.1\%$ in patients vs. $10.7 \pm 4.5\%$ in controls ($p=0.3$).

Wright et al showed that FMD was significantly impaired in SLE patient compared to age and sex matched controls ($p=0.001$).They showed that, altered structure and function of the forearm microcirculation contribute to impaired FMD through a reduction in shear stress stimulus where there FMD was a strong correlation between FMD and diastolic shear stress (DSS) $r=0.65$, $p=0.01$ (17).

Piper et al., found that SLE patients showed significantly impaired endothelial function compared with healthy controls ($p=0.001$) however NMD did not differ between groups.(13)

Our results did not agree with *Palmieri et al, 2008*, who showed that SLE patients had lower FMD than controls (11).

Our results agree with *Aizer et al.*, where there was no statistically significant differences between SLE cases and controls in FMD considered as absolute dilation or as percent dilatation ($P = 0.99$). There was no statistically significant difference between patients or controls as regards NMD. *Aizer et al* results agreed with our results due to the proximal cuff application (18).

Our results regarding the relation between SLE and FMD agree with *Cypine et al 2009*, who studied 30 SLE women (aged 37.45 ± 9.22 years) and 66 control (aged 37.45 ± 8.69).They showed that there was no statistically significant differences between patients and control as regards FMD ($p = 0.67$) and that there are two other markers of arterial wall dysfunction, aortic AIX (augmentation index ;the parameter of systemic arterial stiffness) and to a less extent increased carotid –radial PWV (pulse wave velocity ;the indicator of diminished regional vessel flexibility),but not FMD and they found that both were increased in young SLE women with no history of cardiovascular disease and no severe organ damage when compared to healthy controls ($p=0.004$, 0.036 ,respectively).(19)

It may be assumed that arterial stiffness plays an independent pathogenic role in atherosclerosis and may be responsible for premature atherosclerosis in SLE and atherosclerosis lesions. (20)

In our study, there was no correlation between FMD and disease activity which was assessed in this study using SLEDAI ($r= 0.03$, $p=0.9$) or disease duration ($r= 0.03$, $p= 0.9$)

In contrast to our study ,*Cypine, et al., 2009* reported that FMD showed strong and significant relation with disease duration but their results come along with ours in that SLEDAI as a composite

measure of disease activity had no impact on arterial wall function. Concomitantly, Raynaud phenomenon or anti-phospholipid syndrome had no impact on arterial wall endothelium as well .Moreover,TG and CRP ,which are commonly considered as predictor of cardiovascular risk in general population and were significantly higher in SLE group ,did not show any influence to FMD or AIX (Augmentation index) which was used in that study .Also they showed that endothelium-dependent dilatation was not related to anticardiolipin antibodies, Raynaud s phenomenon, SLE disease activity score (19)

Our results disagree with Wright, et al. who showed that there was a significant negative correlation between disease activity (as measured by SLAM-R) and FMD ($r=0.67$, $p=0.01$) and also a weaker negative association between CRP levels and FMD ($r=0.41$, $p=0.05$). (17)

In our study FMD showed weak but statistically significant negative association between endothelial dysfunction and hypercholesterolemia ($r=-0.3$, $P= 0.05$).

As we didn't find significant difference between patients and controls as regarding FMD%, we tried to find differences between patients themselves dividing them into those with $FMD \geq 10\%$ and those with $FMD < 10\%$ and we did not find significant difference .As *Kuvin, et al., (10)*, *palmieri et al., (11)* stated that endothelial dysfunction is considered significant if $FMD\% < 10$, $FMD\% \geq 10$ however in our study we didn't find any difference between groups.

In a study done by *Palmieri et al* where they selected SLE patients without clinically overt cerebrovascular events (evaluated by cardiac and vascular echo – Doppler techniques) stratified according to organ damage using systemic lupus International collaborating clinics (SLICC) damage index they defined endothelial dysfunction in his study as $FMD/NMD < 0.7$ to increase the sensitivity and specificity of the technique. (11)

In our study $FMD/NMD < 0.7$ ($n = 23$ case (62.2%) and those having $FMN/MND > 0.7$ (38%) we found, no significant differences between them as regarding clinical, laboratory data, and SLEDAI.

As regards carotid intima – media thickness, there was no statistically significant difference between patients and controls ($P = 0.8$) and no correlation between IMT and FMD ($r = 0.03$). This may be contributed to the young age of the patients in the study mean age (24.1 ± 7.6 years) and to short disease duration (2.4 ± 3.3 years)

Unlike other studies which showed increased IMT with the progression of atherosclerosis process reaching highest level in patient with multiple cardiovascular complications. (21) (22) (23)

Our study agrees with *kiss*, (16) whose results did not show significant difference in IMT between lupus patients and control, however they found that IMT increased with progression of atherosclerosis process reaching the highest level in patients having multiple cardiovascular complications. However, in contrast with the publication of EL-Magadmi (12), who found negative correlation between IMT, FMD ($r=-0.37$, $p=0.01$). Kiss et al did not find this correlation which also agreed with our results.

5. Conclusion

Our study revealed that validation of FMD as a measure of endothelial dysfunction and predictor of future cardiovascular events in SLE is lacking despite data suggesting its predictive usefulness in other populations including patients with coronary artery disease and hypertension (24)

Thus we cannot rely on FMD as a solid evidence of the early detection of endothelial dysfunction as Doppler ultrasound is operator dependent and requires a trained sonographer to obtain accurate and reliable serial images of the brachial artery.

Also in the same time we cannot deny the presence of endothelial dysfunction in systemic lupus patients which could not be explained by traditional risk factors of atherosclerosis.

Long term close follow up is recommended, other modalities such as microcirculatory studies may be used.

Recommendation:

Further studies are required to evaluate endothelial dysfunction through measuring arterial wall stiffness. In particular, the pulse wave velocity (PWV) and augmentation index (AI) which determine the elasticity and other properties of the artery which correlate with arterial dispensability and stiffness and microcirculation.

Limitations of the study:

Our study has several limitations. First; the patients included in the study were with low age limit. Second, patients were with short mean duration of the disease. Third, small group of the study.

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