Assessment of Cardiac Function and Subclinical Atherosclerosis in Children with Systemic Lupus Erythematosus

Type
Research paper

Keywords
subclinical atherosclerosis, intima media thickness, Juvenile onset Systemic lupus erythematosus, pulsed wave tissue Doppler

Abstract
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Material and methods
Data about thirty children with SLE following up at Alexandria Main Children Hospital were collected and compared to thirty matched controls. The collected data were about demographic criteria, systemic examination and laboratory findings. However, all participants were subjected to echocardiography, pulsed wave tissue Doppler (PWTD) and sonographic assessment of intima media thickness of abdominal aorta (aIMT) and carotid arteries (cIMT).

Results
The patients group with mean age of 11.3 ± 2 years and mean duration of disease 3.2 ± 2.3 years, included 63.3% (n=19) hypertensive cases with no heart failure. High cholesterol values were reported in 30%. The main findings of the imaging studies of patients showed significantly low ejection fraction (EF) (57.9 ± 5.8 P <0.001) and low mitral annular velocities at septal and lateral walls at peak systole (Sm) and peak early diastolic Filling (Em) (P <0.001). Also there were significant high a IMT (1.1 ± 0.3) and c IMT (0.5 ± 0.7) for patients. The duration of the disease and a IMT were significant risk factors that negatively affect Sm and Em of lateral wall (p ≤ 0.05).

Conclusions
In J SLE, impaired LV function and subclinical atherosclerosis were prevalent specially among children with longer disease duration which highlight the need for periodic checkup by ultrasonography and PWTD.
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Conclusion: In J SLE, impaired LV function and subclinical atherosclerosis were prevalent specially among children with longer disease duration which highlight the need for periodic checkup by ultrasonography and PWTD.

KEYWORDS

Juvenile onset Systemic lupus erythematosus, pulsed wave tissue Doppler, intima media thickness, subclinical atherosclerosis

Abbreviations:

J SLE: Juvenile onset systemic lupus erythematosus

aIMT: intima media thickness of abdominal aorta
INTRODUCTION

Juvenile onset systemic lupus erythematosus (J SLE) is a life-long autoimmune disease that can involve any organ system with a wide range of disease manifestations with significant morbidity and mortality. The 10-year survival rates are now >90%, which is comparable with that of adults because of major advances achieved in the field of pediatric rheumatology [1]. Those children are now surviving into adulthood and have to face many challenges imposed by their chronic illness. Cardiovascular morbidity and mortality are becoming major health concerns for those cases [2]. Cardiovascular involvement has a wide spectrum of presentation ranging from asymptomatic to severe overt conditions. In addition to pericardial, myocardial, valvular and rhythm disturbances a high incidence of coronary artery diseases (CAD) has become a recognized cause of mortality [2, 3]. Chronic inflammation and exposure to corticosteroids create perfect risk factors for endothelial injury and hence, premature atherosclerosis [4]. Clinical cardiovascular involvement has been reported in many studies however, evidence of subclinical involvement is limited to few of them [5].

PATIENTS AND METHODS:

The minimum sample size was calculated based on the smallest effect size between cases and control regarding systolic and diastolic functions of the left ventricle reported by certain study at 2003 [6]. It was equal 50 divided into two equal groups. In order to increase the power of the study, the study was conducted on 60 children (30 with SLE and 30 controls).

This study has the case control design. It was performed between March 2012 and August 2012. The study included thirty children below the age of 16 years diagnosed as SLE and were inactive at time of study (with normal inflammatory markers), the cases were following up for more than 6 months at the pediatric nephrology clinic like the policy of Main Children Hospital of Alexandria University. All active cases were excluded. The patients group at time of diagnosis fulfilled the revised criteria of the American College of Rheumatology for the diagnosis of SLE; The criteria included all the old criteria as photosensitivity, oral ulcers, lupus nephritis while the updated change were in the immunologic disorder category consisted of removal of the LE cell item.
and addition of the anti-phospholipid antibody (aPL), anticardiolipin antibody (aCL), and lupus anticoagulant (LAC) items to positive anti nuclear antibody and anti-double strand [7]. Another thirty children matching in age and sex were selected randomly after getting consent of caregivers. Those were children presented to hospitals with acute minor illness (e.g pneumonia, diarrhea.) excluding cases with chronic medical diseases. Written informed consent were collected from patient’s caregivers, and the local Ethics Committee approved the study protocol. Data of studied groups were retrieved from hospital records about medical history, physical examination, laboratory findings and electrocardiography while echocardiography and vascular sonography were performed for all.

Echocardiography:

Two-dimensional echocardiography, M-mode, and Doppler flow modalities were applied to assess left ventricular function through measuring ejection fraction (EF), fractional shortening (FS) peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), E/A ratio. The normal values for E and A velocities were 0.73±0.09 and 0.38±0.08 m/sec respectively [8]. Pulsed wave tissue Doppler (PWTD) recorded contraction and relaxation velocities of mitral annulus. The highest amplitude signal was evaluated in the apical four-chamber view, a 5-mm tissue Doppler sample volume was placed on the septal and lateral mitral annulus. The positive (Sm) wave represented ventricular systole while negative (Em) and negative (Am) waves represented early and late diastole filling. Echocardiography was performed by single person using a 5 MHz transducer of Madison 990 echocardiography.

Vascular ultrasonography:

Intimal medial wall thickness (IMT) measurements were obtained for the study and control groups though using a Toshiba Nemio Ultrasonic scanner with a 7.5 MHz transducer. Both carotid arteries were scanned 10 mm from the bifurcation of the common carotids. Intimal medial wall thickness of both right and left carotid arteries were measured three times each then the mean value was calculated to represent cIMT of the patient. Meanwhile, abdominal aorta was assessed at anterior and posterior walls and were examined distally until the aortic bifurcation (8mm thickness was the normal cut-off value for the IMT for abdominal aorta) [9].

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Mann Whitney test was used to compare two groups for abnormally distributed quantitative variables. Student t-test was
used for normally distributed quantitative variables, to compare between two studied groups, Pearson coefficient to correlate between two normally distributed quantitative variables, Spearman coefficient to correlate between two distributed quantitative abnormally variables. Significance of the obtained results was judged at the 5% level.

RESULTS:

Patients age at the time of the study ranged from 6 to 15 years (mean 11.3 years ±2.6) with female to male ratio 8/2. The duration of disease ranged 6 months to 9 years (mean 3.2 ± 2.3 year) as in Table I. No significant differences for body mass index (BMI) found between the participants. About 63.3% (n=19) of the cases were hypertensive, eight cases had lower limbs edema (26.6%), four patient had sinus tachycardia, and no cases suffered from overt heart failure. At time of study laboratory data reported anemia among 20% of cases (n=6) with insignificant variations in hemoglobin levels between studied groups. Proteinuria was evidenced among 3 cases. The mean values of serum triglyceride were significantly higher among cases compared to the controls while mean of total cholesterol (TSC) and serum creatinine were within normal for all participants. However, high triglycerides were recorded among 36.3% (n=11cases) and high TSC was reported among 30% (n=9 cases). Renal biopsy specimens were analyzed for (n=26) and showed a wide range of pathologic changes. According to modified WHO classification of glomerular lesions [10]; class I; minimal mesengial lupus nephritis, class II: mesengial proliferative lupus nephritis, class III; focal lupus nephritis, class IV; diffuse lupus nephritis, class V; membranous lupus nephritis and class IV; advanced sclerosis lupus nephritis. There were class IV in eleven patients, class II- eight, class III in 4 and class V in 3 cases. All cases were on prednisone dose ranging between 0.2-2 (mean 0.8 mg/Kg/day).

Cardiac function:

Although the mean of EF and FS of patients group were within normal limits (EF. 57.9 ± 5.8 and FS: 33.1 ± 3.5), they were significantly lower than controls (EF: 67.8 ± 4.7and FS: 37.8 ± 3.4, P <0.001). EF values were abnormally low in 6 patients (20%). Left ventricular diastolic functions were also impaired with significant decreased E wave (80.5 ± 5.1versus 92.6 ± 7.6 p<0.001) and decreased E/A ratio (1.5 ± 0.1 versus 1.6 ± 0.2, p = 0.003). While peak A velocity increased significantly (58 ± 5.9, versus 54.7 ± 4.5, P=0.017) as shown table II. Meanwhile, PWTD findings showed that the mitral annular velocities at septal and lateral walls (Sm sep, Sm
lat) during systole was significantly lower for patients group (10.3 ± 1.8 and 8.3 ± 1.1) compared to controls (11.8 ± 1.3 and 8.7 ± 0.8, p<0.001). Also, mitral annular velocities during diastole (Sm sep, Sm lat, E sept, E lat, Em/Am sept and Em/Am lat) were significantly lower for patients compared to controls (p<0.001) as summarized in table II. However, the E/Em ratio was significantly higher among patient’s groups. Our study revealed that some PWTD parameters (Sm lat, Sm sep and Em lat) showed significant negative correlations to the duration of the disease (r=-0.565, P=0.001; r=-0.466, P=0.009) While no significant correlation to total serum cholesterol or to the age as shown in table III. Hypertensive subgroup had significant higher values in Em/Am ratio of septal wall when compared to controls. Table VI.

**Vascular sonography:**

The mean values of a IMT (1.1 ± 0.3) were significantly higher in children with SLE in comparison to controls (0.7 ± 0.1, P<0.001). About 63.3% of cases (n=19) had abnormal aIMT (>0.8mm). Table 2. A significant positive correlation was reported between average of aIMT and duration of the disease (r=0.644, P<0.001) and hypertension (p =0.044) as summarized in tables 3 and 4. Despite, the mean values of c IMT (0.5 ± 0.7) were significantly higher than controls, high values were detected among 30% of the patients. Lastly, there were significant negative correlation between the mitral annular velocities (Sm lat), (Em) and aIMT (r=-0.657, P< 0.001; r=-0.506, P <0.004 respectively) which were displayed in scattered figure 1 (A) and (B) quadrants. However, c IMT showed insignificant correlations to same parameters as shown in Figure 1 (C) and (D) quadrants.
Table: I. Comparison between the two studied groups according to demographic data and laboratory profile of the studied groups.

|                                | Cases (n = 30) | Control (n = 30) | P   |
|--------------------------------|----------------|------------------|-----|
| Age (6-15 years)               | 11.3 ± 2.6     | 10.8 ± 2.99      | 0.466 |
| Gender                         |                |                  |     |
| Male                           | 6 (20%)        | 4 (13.3%)        | 0.488 |
| Female                         | 24 (80%)       | 26 (86.7%)       |     |
| Duration of disease            | 3.2 ± 2.3      |                  |     |
| BMI (kg/m²)                    | 21.7 (15.3 – 35.7) | 20.6 (5 – 23.7) | 0.147 |
| Hg level                       | 13.2 (9.5 – 15.1) | 12.8 (11.9 – 14.5) | 0.454 |
| **No anemia**                  | 24 (80%)       |                  |     |
| Positive                       | 6 (20%)        |                  |     |
| Cholesterol                    | 186.3 ± 43     | 142.4 ± 21.8     | 0.254 |
| TG                             | 125 (43 – 270) | 99.5 (65 – 143)  | 0.006* |
| Creatinine                     | 0.50 ± 0.10    | 0.46 ± 0.08      | 0.084 |

* Statistically significant at p ≤ 0.05

**Criteria of anemia according to age group; from 5-12-year Hg < 11.5 g/dl, from 12-14 year Hg < 12 g/dl. Age >15-year girl Hg < 12g/dl. age >15 year boys Hg < 13g/dl. reference [30].
Table: I. Comparison between the two studied groups according to parameters of standard echocardiography, pulsed tissue Doppler and vascular sonography.

|                          | Cases (n=30) | Control (n=30) | p       |
|--------------------------|--------------|----------------|---------|
| **Echocardiography**     |              |                |         |
| EF                       | 57.9 ± 5.8   | 67.8 ± 4.7     | <0.001* |
| <55 Abnormal             | 6 (20%)      | 0 (0%)         | 0.024*  |
| FS                       | 33.1 ± 3.5   | 37.8 ± 3.4     | <0.001* |
| <29 Abnormal             | 4 (13.3%)    | 0 (0%)         |         |
| E                        | 80.5 ± 5.1   | 92.6 ± 7.6     | <0.001* |
| A                        | 58 ± 5.9     | 54.7 ± 4.5     | 0.017*  |
| E/A                      | 1.5 ± 0.1    | 1.6 ± 0.2      | 0.003*  |
| **PWTD (Mitral annulus)**|              |                |         |
| Lateral wall MA          |              |                |         |
| Sm lat                   | 10.3 ± 1.8   | 11.8 ± 1.3     | <0.001* |
| Em lat                   | 14.9 ± 1.7   | 18.2 ± 18.2    | <0.001* |
| Am                       | 9.3 ± 0.7    | 9.1 ± 0.8      | 0.361   |
| Em/Am                    | 1.6 ± 0.2    | 2 ± 0.2        | <0.001* |
| E/Em                     | 6.3 ± 1.1    | 4.4 ± 0.4      | <0.001* |
| Septal wall MA           |              |                |         |
| Sm sep                   | 8.3 ± 1.1    | 8.7 ± 0.8      | 0.219   |
| Em sep                   | 13.5 ± 1.5   | 15.2 ± 0.6     | <0.001* |
| Am sep                   | 9.1 ± 0.7    | 8.2 ± 0.5      | <0.001* |
| ES/AS                    | 1.5 ± 0.2    | 1.9 ± 0.1      | <0.001* |
| c IMT                    | (0.4 – 0.7)  | (0.4 – 0.5)    | 0.041*  |
| Mean ± SD.               | 0.5 ± 0.7    | 0.5 ± 0.1      |         |
| Abnormal >0.55           | 9 (30%)      | 0 (0%)         |         |
| a IMT                    | (0.5 – 1.7)  | (0.5 – 0.8)    | <0.001* |
| Mean ± SD.               | 1.1 ± 0.3    | 0.7 ± 1.1      |         |
| > 0.8 Abnormal           | 19 (63.3%)   | 0 (0%)         |         |

*: Statistically significant at p ≤ 0.05.
E: early diastolic filling velocity (cm/s); A: late diastolic filling velocity (cm/s); E/A ratio: early (E) to late (A) ventricular filling velocities; EF: ejection fraction; PWD: pulsed wave Doppler; Sm: peak velocity of contraction wave. Em: peak velocity early of relaxation wave. Am: peak velocity late of relaxation wave. Lat: lateral wall. Sep: septal wall. cIMT: carotid intimal medial thickness.
Table: III. Correlation of risk factors versus tissue Doppler findings and abdominal aorta IMT among cases group

|                        | Sm lat | Em lat | Em/Am lat | Sm sep | Em sep | Em/Am sep | a IMT |
|------------------------|--------|--------|-----------|--------|--------|-----------|-------|
| Age (years)            | r      | p      | r         | p      | r      | p         |       |
|                        | -0.289 | 0.121  | -0.342    | 0.065  | 0.107  | 0.178     | 0.127 |
| Duration of disease    |        |        |           |        |        |           |       |
|                        | r      | p      | r         | p      | r      | p         |       |
|                        | -0.565*| 0.001* | -0.466*   | 0.009* | -0.261 | 0.164     | 0.318 |
| Cholesterol            | r      | p      | r         | p      | r      | p         |       |
|                        | -0.070 | 0.715  | 0.079     | 0.680  | 0.283  | 0.130     | 0.935 |
| Maintenance dose of    | r      | p      | r         | p      | r      | p         |       |
| corticosteroids        |        |        |           |        |        |           |       |
|                        | -0.016 | 0.933  | 0.409*    | 0.025* | 0.347  | 0.060     | 0.026*|

r: Pearson coefficient
*: Statistically significant at p ≤ 0.05

Table: VI. Relation between hypertension with different echo and sonography parameters in cases group

| Hypertension | Sm lat | Em lat | Em/Am lat | Sm sep | Em sep | Em/Am sep | a IMT |
|--------------|--------|--------|-----------|--------|--------|-----------|-------|
| No (n= 11)   | 10.5 ± 1.4 | 14.7 ± 1.7 | 1.5 ± 0.2 | 8.3 ± 0.9 | 13 ± 1.8 | 1.4 ± 0.2 | 0.8 (0.5 – 1.3) |
| Yes (n= 19)  | 10.2 ± 2  | 15.1 ± 1.7 | 1.7 ± 0.2 | 8.4 ± 1.2 | 13.8 ± 1.3 | 1.6 ± 0.2 | 1.1 (0.7 – 1.7) |

p: Statistically significant at p ≤ 0.05
Figure 1. A-Correlation between a IMT with Sm lat among cases group. B-Correlation between a. IMT with Em lat among cases group. C-Correlation between c IMT with Sm lat among cases group. D-Correlation between c. IMT with Em lat in cases group.

A                                                                 B

C                                                                        D
DISCUSSION:

Studying cardiovascular changes in children with SLE become challenging over the past decade. The current study, focused on assessing the cardiac function of J SLE by different modalities of echocardiography and on detecting silent atherosclerotic changes by sonography. Also, the study assessed the risk factors of these cardiovascular changes as age of onset, duration of the disease, BMI, hypertension, dyslipidemia, renal pathology and dose of corticosteroid. Most of the enrolled patients (80%) were females similar to the literature and many studies [3, 5, 6]. The age of onset of disease for most of our cases were above 5 years except tow cases (3 and 4 years about 6.6%) and this was found by another study [6] which reported that the occurrence of the disease below 5 years is rare. Body mass indices of patients were within the normal limits similar to results of Brazilian study [11] at 2014 where the median of patients was close to controls (21.74 kg/m^2 versus 21.43). An Omansi study assessed BMI concluded that the growth failure is an important determinant of disease damage, high steroid dose and longer disease duration [12].

Clinically, non of the cases were suffering from heart failure, and about tow thirds developed hypertension. It is higher percent compared to that found by previous study [13] who reported that about 25% of cases developed hypertension before age of 18 years but hypertension could be caused by renal disease and or long-term high-dose corticosteroid. Captopril and atenolol were the used antihypertensive medications. In our study, renal involvement was 100 % among cases performed renal biopsy (n=26/30) with different classes of renal pathology and this may explain high percent of hypertensive patients. However, 57.8% of them were controlled. In concordant to some studies [6, 14] arrhythmia was positive among 10 % of cases which was documented by ECG to be sinus tachycardia.

Laboratory data at time of study revealed that about one third of patient had elevated levels of serum cholesterol and triglycerides however, triglycerides levels were significantly higher in patients when compared to controls. This matched the pattern of dyslipidemia described by other studies over the adults with SLE [15] and over children by [16] who reported also high level of LDL and low levels of HDL among the patients. That might be attributed to the used medications like corticosteroids and atenolol (old beta-blockers) which was reported by some studies to raise serum triglyceride [17]. In our study, renal function for all the patients were normal.

Echocardiographic evaluations of cardiac function were performed for the studied groups. Parameters of
systolic function by standard modalities (EF and FS) were significantly lower in patients than controls. However, they were within normal and 20% of cases had abnormal EF. The diastolic function was impaired through significantly low E wave in patients compared to controls while A wave increased and E/A ratio decreased significantly but remained within normal. This was consistent to results found by many studies which explained the asymptomatic systolic and diastolic function impairment by lupus myocarditis (immunopathological changes of heart) [6,15].

Recently, PWTD have been used as a sensitive method for evaluation of cardiac performance. It relies on determining the contraction and relaxation velocities of the myocardium through assessing mitral annular velocities. Therefore, PWTD can evaluate global, regional and longitudinal myocardial contraction which may be involved sub clinically. In contrast to EF which evaluates the heart globally [18] The present study recorded regional defects in systolic and diastolic function of lateral wall of mitral annulus and impaired diastolic function of septal wall. As the average of mitral annular velocities at (Sm lat) was significantly decreased in patients compared to controls while septal wall velocities (Sm sep) were insignificantly diminished. Moreover, diastolic indices (Em sep, Em late, Em/Am latel and E/Em lat) at septal and lateral walls were significantly lower in patients group.

Actually, due to paucity of similar studies over children, we compared our results to similar studies performed over adults with SLE which come in agreement with our results by finding significant impairment of regional wall function of the heart whether systolic or diastolic indices [19]. More over, it matched the results of concluded by Turkish study over children with familial Mediterranean fever (FMF) taking in consideration that both SLE and FMF are long lasting diseases based on immune dysregulation [20]. The asymmetry of the results as far as lateral wall compared to septal wall velocities may be explained by autoimmune inflammation in lupus cardities that reported similiary in viral myocarditis studies to have preference of lateral wall abnormalities (85%) rather than septal wall (31%) [21]. This could be attributed to relation between inflammation and tissue perfusion in which septal wall basically receives blood supply from right and left coronaries while lateral wall is supplied only by lateral circumflex [21]. In agreement with recent study over lupus children, lateral wall regional changes were detected during active and inactive phases of the disease [22].

The current study correlated some risk factors with parameters PWTD. Duration of the disease was an important factor. The longer the duration of the disease, the more reduction in systolic and or diastolic function of heart especially lateral wall of the LV (Sm lat, Em lat, Sm sep). It was not only the longevity of the illness,
our study referred also to age of onset of the disease as 100% of cases who developed SLE below 5 years had abnormal diastolic function (E/A<1, Em/Am<1) although they had variable duration of illness (5, 6,7 years).

On the other side, maintenance dose of corticosteroid given during the inactive state was not correlated to regional cardiac wall velocities except early diastolic filling waves of lateral and septal walls were directly related. This may refer to significant anti-inflammatory effect of steroids on improving diastolic wave velocities. Hypertension as risk factor for cardiac changes was only correlated to Em/Am ratio of septal wall; less ratio than controls as sign of of impaired diastolic function. Small sample size might be cause of absence of other correlations, the effect of hypertension deserve further investigations with larger samples of lupus hypertensive children. The current results over pediatric patients were consistent to another Egyptian study performed over adult SLE at 2013 [23].

Apart of cardiac involvement, acceleration of vascular changes is considered another serious complication for J SLE. The reason of premature atherosclerosis is unknown. The leading theory is that immune complex deposition over the vessels causes the initial intimal damage which trigger vascular change [24]. lupus is now considered to be an independent risk factor for the development of atherosclerosis which enhance the development of coronary artery disease during adulthood.

The current study revealed that a IMT and c IMT were significantly higher among patients compared to controls. This matched some studies used IMT as surrogate non invasive early sonographic marker for atherosclerosis [25, 26].

Silent atherosclerotic changes were detected among tow thirds of the patients by abnormal a IMT in comparison to one third of cases had abnormal cIMT. That was consistent to previous studies [9, 27] which concluded that abdominal aorta is an earlier site r vascular changes in children. Our results revealed that hypertension was potential risk factor for higher values of aIMT matched with others [28]. A potent significant negative correlation was found between in aIMT and between (Sm lat, Em lat) done by tissue Doppler. The higher the values of aIMT (atherosclerosis) the lower the cardiac indices (impaired function). This may be the first study to publish this correlation among pediatric patients. This was consistent with a Brazilian study at 2010 performed on adult females with subclinical atherosclerosis and they found that carotid IMT had negative correlations with tissue Doppler indices of diastolic function [29]. This referee to effect of atherosclerosis on impairing cardiac function as it may enhance arterial stiffness of major arteries, such as the carotid artery and
aorta, increasing afterload to the left ventricle, with a negative impact on diastolic function. This highlights the importance of screening and controlling subclinical vascular changes for better long-term cardiac performance.

CONCLUSION:

Juvenile onset SLE children are at high risk for silent impairment of cardiac function and premature atherosclerosis. Regular follow-up of global cardiac function and regional myocardial performance is highly recommended not only by echocardiography but also with Tissue Doppler modality. Periodic check-up of IMT of abdominal aorta is a good marker for detecting subclinical atherosclerosis, especially for children with long duration for the disease, hypertension, high maintained dose of corticosteroid, and/or abnormal echocardiographic parameters of cardiac function.

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Conflict of interest

The authors declare no conflicts of interest.

Compliance with Ethical Standards

REFERENCES:

1) Doria A, Iaccarino L, Ghirardello A, Zampieri S, Arienti S and Sarzi-Puttini P. Long-term prognosis and causes of death in systemic lupus erythematosus. Am J Med. 2006; 119:700–6.

2) Barsalou J, Bradley T J and Silverman ED. Cardiovascular risk in pediatric-onset rheumatological diseases. Arthritis Research & Therapy 2013; 15:212.

3) Mavrogeni S1, Servos G, Smerla R, Markoussis-Mavrogenis G, Grigoriadou G and Kolovou G. Cardiovascular involvement in pediatric systemic autoimmune diseases: the emerging role of noninvasive cardiovascular imaging. Inflamm Allergy Drug Targets. 2015; 13:371-1.

4) Stojan G and Petri M Atherosclerosis in Systemic Lupus Erythematosus. J Cardiovasc Pharmacol. 2013; 62: 255–62.
5) H-T Chung, Y-L Huang, K-W Yeh and J-L Huang Subclinical deterioration of left ventricular function in patients with juvenile-onset systemic lupus erythematosus. Lupus 2015; 24: 3.

6) Günsal N, Kara N, Akkök N, Çakar N, Kahramanyol O and Akalýn N. Cardiac abnormalities in children with systemic lupus erythematosus. Turkish Journal of Pediatrics 2014; 45: 301-5.

7) Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 2003 1; 40: 17-25.

8) Kimball TR and Meyer RA. Echocardiography. In: Allen HD (ed). Moss and Adams’ Heart Disease in Infants, Children and Adolescents 6th ed. Philadelphia: Lippincott Williams and Wilkins 2001; 1: 252-62.

9) Davis PH, Dawson JD, Blecha B, Mastbergen RK and Sonka M. Measurement of Aortic Intimal-Medial Thickness in Adolescents and Young Adults. Ultrasound in med bio J 2010; 36: 560-5.

10) Weening JJ, D’Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB et al. The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. JASN 2004; 2: 241-50

11) Sinicato NA, Postal M, Peres FA, Peliçari K, Marini R, Santos ADO et al. Obesity and Cytokines in Childhood-Onset Systemic Lupus Erythematosus. J of Immunolo Research 2014 Article ID 162047, 6 pages http://dx.doi.org/10.1155/2014/162047

12) Abdalla E, Jeyaseelan L, Ullah I and Abdwani R. Growth Pattern in Children with Systemic Lupus Erythematosus. Oman Med J 2017;32: 284-90.

13) Ostrove BE, Eichenfild AH, Goldsmith DP, Kaplan B and Atheya B. Hypertension in children with systemic lupus erythematosus. Seminars in Arthritis and Rheumatism 1989;19: 90-8

14) Ahmed A and El Shama M Asymptomatic Cardiac Involvement in Children with Systemic Lupus Erythematosus. Journal of medical sciences 2006; 6: 944-49.
15) Yuan J, Li LI, Wang Z, Song W and Zhang Z. Dyslipidemia in patients with systemic lupus erythematosus: Association with disease activity and B-type natriuretic peptide levels. Biomed Rep 2016;4 :68-72.

16) Ortiz TT, Terreri MT, Caetano M, Souza FS, D'Almeida V, Sarni RO and Hilário MO. Dyslipidemia in pediatric systemic lupus erythematosus: the relationship with disease activity and plasma homocysteine and cysteine concentrations. Ann Nutr Metab 2013; 63: 77-82.

17) Nandeesha H, Pavithran P, Madanmohan T. Effect of antihypertensive therapy on serum lipids in newly diagnosed essential hypertensive men. Angiology. 2009; 60: 217–20.

18) Kadappu KK and Thomas L. Tissue Doppler Imaging in Echocardiography: Value and Limitations. Heart and Lung Circulation 2015; 24: 224–33.

19) Elnady BM, Abdelghafar AS, Khalik ES, Algethami MM, Basioni AS, Al-Otaibi MD et al. The implication of tissue Doppler echocardiography and cardiopulmonary exercise in early detection of cardiac dysfunction in systemic lupus erythematosus patients. Eur J Rheumatol. 2016 ; 3 :109-17.

20) Ceylan Ö1, Özgür S, Örün UA, Doğan V, Yılmaz O and Keskin M. Assessment of left ventricular functions with tissue Doppler, strain, and strain rate echocardiography in patients with familial Mediterranean fever. Anatol J Cardiol 2015 .15: 663-8.

21) Li YD, Hsiao FT, Lai CP and Chen CW. Acute Viral Myocarditis Mimicking ST Elevation Myocardial Infarction: Manifestation on Cardiac Magnetic Resonance. Case report. Acta Cardiol Sin 2010; 26: 44

22) Khositseth A, Prangwatanagul W, Tangnararatchakit K, Vilaiyuk S, Su-Angka N. Myocardial performance index in active and inactive paediatric systemic lupus erythematosus. Clin Exp Rheumatol. 2017; 35: 344-50. Epub 2017 Feb 3.

23) Allama N, Darweech HE, Hamadanallha N and Ashour Z Evaluation of left ventricular myocardial function in Egyptian patients with systemic lupus erythematosus: Tissue Doppler study and its relation to disease activity the Egyptian. Rhematologist 2013; 35: 217-23.
24) Zeller CB and Appenzeller S. Cardiovascular Disease in Systemic Lupus Erythematosus. The Role of Traditional and Lupus Related Risk Factors. Curr Cardiol Rev 2008; 4:116-22.

25) Quinlan C, Kari J, Pilkington C, Deanfield J, Shroff R and Marks ST. The vascular phenotype of children with systemic lupus erythematosus. Pediatr Nephrol 2015; 30:1307–16.

26) Sozeri B, Deveci M, Dincel N and Mir S. The early cardiovascular changes in pediatric patients with systemic lupus erythematosus. Pediatr Nephrol 2013; 28:471–76.

27) Järvisalo MJ, Jartti L, Salonen KN, Irla K, Rönemaa T, and Hartiala JJ. Increased Aortic Intima-Media Thickness A Marker of Preclinical Atherosclerosis in High-Risk Children. Circulation 2001; 29: 43-7.

28) Boros CA, Bradley TJ, Cheung MM, Bargman JM, Russell JL, McCrindle BW et al. Early determinants of atherosclerosis in pediatric systemic lupus erythematosus. Clin Exp Rheumatol 2011; 29: 575-81.

29) Garcia MMO, Rodrigues MG, Neto JAD and Correia LC. Influence of subclinical atherosclerosis on diastolic function in individuals free of cardiovascular disease. Arq. Bras. Cardiol 2011: 95; 473-8.

30) WHO, UNICEF, UNU. Iron deficiency anemia: assessment, prevention and control, a guide for programme managers. Geneva, World Health Organization, 2001.
Table I: Comparison between the two studied groups according to demographic data and laboratory profile of the studied groups.

|                          | Cases (n = 30) | Control (n = 30) | p     |
|--------------------------|---------------|-----------------|-------|
| Age (6-15years)          | 11.3 ± 2.6    | 10.8 ± 2.99     | 0.466 |
| Gender                   |               |                 |       |
| Male                     | 6 (20%)       | 4 (13.3%)       | 0.488 |
| Female                   | 24 (80%)      | 26 (86.7%)      |       |
| Duration of disease      | 3.2 ± 2.3     |                 |       |
| Mean and SD (y)          |               |                 |       |
| BMI (kg/m²)              | 21.7 (15.3 – 35.7) | 20.6 (5 – 23.7) | 0.147 |
| Hg level                 | 13.2(9.5 – 15.1) | 12.8(11.9 – 14.5) | 0.454 |
| **No anemia**            | 24 (80%)      |                 |       |
| Positive                 | 6 (20%)       |                 |       |
| Cholesterol              | 186.3 ± 43    | 142.4 ± 21.8    | 0.254 |
| TG                       | 125(43 – 270) | 99.5(65 – 143)  | 0.006*|
| Creatinine               | 0.50 ± 0.10   | 0.46 ± 0.08     | 0.084 |

*: Statistically significant at p ≤ 0.05

**Criteria of anemia according to age group; from 5- 12-year Hg < 11.5 g/dl, from 12-14 year Hg < 12 g/dl. Age >15-year girl Hg < 12g/dl. age >15 year boys Hg < 13g/dl, reference [30].
Table II: Comparison between the two studied groups according to parameters of standard echocardiography, pulsed tissue Doppler and vascular sonography.

|                          | Cases (n=30) | Control (n=30) | p       |
|--------------------------|--------------|----------------|---------|
| **Echocardiography**     |              |                |         |
| EF                       | 57.9 ± 5.8   | 67.8 ± 4.7     | <0.001* |
| <55 Abnormal             | 6 (20%)      | 0 (0%)         | 0.024*  |
| FS                       | 33.1 ± 3.5   | 37.8 ± 3.4     | <0.001* |
| <29 Abnormal             | 4 (13.3%)    | 0 (0%)         |         |
| E                        | 80.5 ± 5.1   | 92.6 ± 7.6     | <0.001* |
| A                        | 58 ± 5.9     | 54.7 ± 4.5     | 0.017†  |
| E/A                      | 1.5 ± 0.1    | 1.6 ± 0.2      | 0.003*  |

**PWTD (Mitral annulus)**

|                          |              |                |         |
|--------------------------|--------------|----------------|---------|
| **Lateral wall MA**      |              |                |         |
| Sm lat                   | 10.3 ± 1.8   | 11.8 ± 1.3     | <0.001* |
| Em lat                   | 14.9 ± 1.7   | 18.2 ± 1.2     | <0.001* |
| Am                       | 9.3 ± 0.7    | 9.1 ± 0.8      | 0.361   |
| Em/Am                    | 1.6 ± 0.2    | 2 ± 0.2        | <0.001* |
| E/Em                     | 6.3 ± 1.1    | 4.4 ± 0.4      | <0.001* |
| **Septal wall MA**       |              |                |         |
| Sm sep                   | 8.3 ± 1.1    | 8.7 ± 0.8      | 0.219   |
| Em sep                   | 13.5 ± 1.5   | 15.2 ± 0.6     | <0.001* |
| Am sep                   | 9.1 ± 0.7    | 8.2 ± 0.5      | <0.001* |
| ES/AS                    | 1.5 ± 0.2    | 1.9 ± 0.1      | <0.001* |
| **c IMT**                | 0.4 – 0.7    | 0.4 – 0.5      | 0.041†  |
| Mean ± SD.               | 0.5 ± 0.7    | 0.5 ± 0.1      |         |
| Abnormal >0.55           | 9 (30%)      | 0 (0%)         |         |
| **a IMT**                | 0.5 – 1.7    | 0.5 – 0.8      | <0.001* |
| Mean ± SD.               | 1.1 ± 0.3    | 0.7 ± 0.1      |         |
| > 0.8 Abnormal           | 19 (63.3%)   | 0 (0%)         |         |

*: Statistically significant at p ≤ 0.05

E: early diastolic filling velocity (cm/s); A: late diastolic filling velocity (cm/s); E/A ratio: early (E) to late (A) ventricular filling velocities; EF: ejection fraction; PWD: pulsed wave Doppler; Sm: peak velocity of contraction wave. Em: peak velocity early of relaxation wave. Am: peak velocity late of relaxation wave. Lat: lateral wall. Sep: septal wall. cIMT: carotid intimal medial thickness
Table III. Correlation of risk factors versus tissue Doppler findings and abdominal aorta IMT among the cases group (n= 30)

|                        | Sm lat | Em lat | Em/Am lat | Sm sep | Em sep | Em/Am sep | a IMT  |
|------------------------|--------|--------|-----------|--------|--------|-----------|--------|
| Age (years)            | r      | p      | r         | p      | r      | p         | r      |
|                        | -0.289 | 0.121  | -0.342    | 0.065  | -0.107 | 0.574     | 0.342  |
|                        | -0.253 | 0.178  | -0.285    | 0.127  | -0.073 | 0.702     | 0.285  |
|                        | 0.294  | 0.702  | 0.115     |        |        |           |        |
| Duration of disease    | r      | p      | r         | p      | r      | p         | r      |
|                        | -0.565* | 0.001* | -0.466*   | 0.009* | -0.261 | 0.164     | 0.146  |
|                        | -0.440* | 0.015* | -0.440    | 0.003* | -0.189 | 0.318     | 0.863  |
|                        | -0.033 | 0.318  | 0.644*    |        |        |           |        |
| Cholesterol            | r      | p      | r         | p      | r      | p         | r      |
|                        | -0.070 | 0.715  | 0.079     | 0.680  | 0.283  | 0.130     | 0.873  |
|                        | 0.030  | 0.873  | 0.016     | 0.935  | 0.193  | 0.307     | 0.941  |
|                        | 0.149  |        |           |        |        |           |        |
| Maintenance dose of    | r      | p      | r         | p      | r      | p         | r      |
| corticosteroids        | -0.016 | 0.933  | 0.409*    | 0.025* | 0.347  | 0.989     | 0.026* |
|                        | 0.060  | 0.141  | 0.026*    | 0.141  | 0.989  | 0.461     |        |

r: Pearson coefficient
*: Statistically significant at p ≤ 0.05

Table VI: Relation between hypertension with different echo and sonography parameters in cases group (n= 30)

| Hypertension       | No (n= 11)  | Yes (n= 19) | p   |
|--------------------|-------------|-------------|-----|
| Sm lat             | 10.5 ± 1.4  | 10.2 ± 2    | 0.721|
| Eml at             | 14.7 ± 1.7  | 15.1 ± 1.7  | 0.522|
| Em/Am lat          | 1.5 ± 0.2   | 1.7 ± 0.2   | 0.096|
| Sm sep             | 8.3 ± 0.9   | 8.4 ± 1.2   | 0.902|
| Em sep             | 13 ± 1.8    | 13.8 ± 1.3  | 0.164|
| Em/Am sep          | 1.4 ± 0.2   | 1.6 ± 0.2   | 0.010*|
| a IMT              | 0.8 (0.5 – 1.3) | 1.1 (0.7 – 1.7) | 0.044*|

*: Statistically significant at p ≤ 0.05
Figure 1. A- Correlation between a IMT with Sm lat among cases group. B- Correlation between a. IMT with Em lat among cases group. C- Correlation between c IMT with Sm lat among cases group. D- Correlation between c. IMT with Em lat in cases group.
